

(19)



(11)

**EP 1 618 087 B1**

(12)

**EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention  
of the grant of the patent:  
**13.06.2012 Bulletin 2012/24**

(51) Int Cl.:  
**C07C 233/00** <sup>(2006.01)</sup> **A61K 31/16** <sup>(2006.01)</sup>  
**A61K 31/165** <sup>(2006.01)</sup> **A61P 31/00** <sup>(2006.01)</sup>  
**A61P 31/04** <sup>(2006.01)</sup>

(21) Application number: **04700887.5**

(86) International application number:  
**PCT/US2004/000433**

(22) Date of filing: **08.01.2004**

(87) International publication number:  
**WO 2004/062601 (29.07.2004 Gazette 2004/31)**

(54) **ANTIBACTERIAL AGENTS**

ANTIBAKTERIELLE MITTEL

AGENTS ANTIBACTERIENS

(84) Designated Contracting States:  
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR  
HU IE IT LI LU MC NL PT RO SE SI SK TR**

(30) Priority: **08.01.2003 US 438523 P**  
**30.04.2003 US 466974 P**  
**13.11.2003 US 520211 P**

(43) Date of publication of application:  
**25.01.2006 Bulletin 2006/04**

(60) Divisional application:  
**10179798.3 / 2 295 402**

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**Description****FIELD OF THE INVENTION**

**[0001]** This invention pertains generally to compounds for use in treating infections in particular caused by gram-negative bacteria. More specifically, the invention described herein pertains to compounds for use in treating gram-negative infections by inhibiting activity of UDP-3-O-(R-3-hydroxydecanoyl)-N-acetylglucosamine deacetylase (LpxC). The present invention provides small molecule inhibitors of LpxC, pharmaceutical formulations containing such inhibitors, compounds for use in treating patients, and to methods of preparing such pharmaceutical formulations. The inhibitors can be used to treat Gram-negative infections of patients alone and in combination with other antibacterials.

**BACKGROUND OF THE INVENTION**

**[0002]** Over the past several decades, the frequency of antimicrobial resistance and its association with serious infectious diseases have increased at alarming rates. The increasing prevalence of resistance among nosocomial pathogens is particularly disconcerting. Of the over 2 million nosocomial infections occurring each year in the United States, 50 to 60% are caused by antimicrobial-resistant strains of bacteria. This high rate of resistance increases the morbidity, mortality, and costs associated with nosocomial infections. In the United States, nosocomial infections are thought to contribute to or cause more than 77,000 deaths per year and cost approximately \$5 to \$10 billion annually. Among Gram-positive organisms, the most important resistant pathogens are methicillin- (oxacillin-) resistant *Staphylococcus aureus*,  $\beta$ -lactam-resistant and multidrug-resistant pneumococci, and vancomycin-resistant enterococci. Important causes of Gram-negative resistance include extended-spectrum  $\beta$ -lactamases (ESBLs) in *Klebsiella pneumoniae*, *Escherichia coli*, and *Proteus mirabilis*, high-level third-generation cephalosporin (Amp C)  $\beta$ -lactamase resistance among *Enterobacter* species and *Citrobacter freundii*, and multidrug-resistance genes observed in *Pseudomonas aeruginosa*, *Acinetobacter*, and *Stenotrophomonas maltophilia*. (Jones RN 2001 Chest 119 (supplement), 397S-404S: Resistance patterns among nosocomial pathogens: Trends over the past few years.)

**[0003]** The problem of antibacterial resistance is compounded by the existence of bacterial strains resistant to multiple antibacterials. For example, *Pseudomonas aeruginosa* isolates resistant to fluoroquinolones are virtually all resistant to additional antibacterials (Sahm DF et al 2001 Antimicrobial Agents and Chemotherapy 45, 267-274: Evaluation of current activities of fluoroquinolones against gram-negative bacilli using centralized in vitro testing and electronic surveillance.)

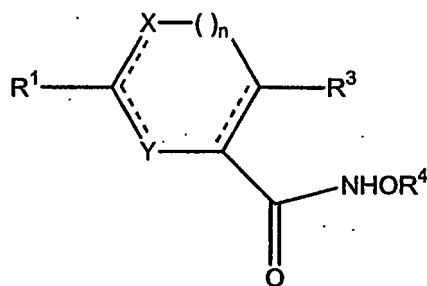
**[0004]** Thus there is a need for new antibacterials, particularly antibacterials with novel mechanisms of action. Most of the antibacterial discovery effort in the pharmaceutical industry is aimed at development of drugs effective against gram-positive bacteria. However, there is also a need for new gram-negative antibacterials. Gram-negative bacteria are in general more resistant to a large number of antibacterials and chemotherapeutic agents than are gram-positive bacteria. A survey of recently reported antibacterials of natural origin showed that over 90% lacked activity against *Escherichia coli*, although they were active against gram-positive bacteria. The outer membrane of gram-negative bacteria contributes to this intrinsic resistance by acting as an efficient permeability barrier, because the narrow porin channels limit the penetration of hydrophilic solutes and the low fluidity of the lipopolysaccharide leaflet slows down the inward diffusion of lipophilic solutes. A second mechanism contributes to the intrinsic resistance of gram-negative bacteria. Recent studies showed that multiple drug efflux pumps, sometimes with unusually broad specificity, act as this second factor to create the general intrinsic resistance of gram-negative bacteria. When their expression levels are elevated as a consequence of physiological regulation or genetic alteration, they can frequently produce impressive levels of resistance to a wide variety of antimicrobial agents. (Nikaido H 1998 Clinical Infectious Diseases 27(Suppl 1), S32-41: Antibacterial resistance caused by gram-negative multidrug efflux pumps.)

**[0005]** Historically, most development of antimicrobial agents has been relatively empirical. Active compounds have generally been found via screening soil, sewage, water, and other natural substances to detect antimicrobial-producing organisms, or by screening various chemical compounds. Once a leading candidate has been found and its chemical structure determined, a series of analogs is made to identify an optimal compound for further clinical development. A more rational approach involves the defining of new targets, such as genes or enzymatic functions, responsible for a crucial cellular essential activity. Once this has been done, inhibitors or blockers of the function or gene product can be developed.

**[0006]** In order to identify potential targets for novel gram-negative antibacterial agents, studies aimed at identifying all essential and important genes in *Pseudomonas aeruginosa* have been performed. Among the essential genes identified was *lpxC*, that encodes the enzyme uridyldiphospho-3-O-(R-hydroxydecanoyl)-N-acetylglucosamine deacetylase (LpxC). This enzyme is the first committed step in the synthesis of lipid A, the lipid moiety of lipopolysaccharide, that is an essential component of all gram-negative bacteria. It therefore is an attractive target for novel antibacterials. In order to be useful as antibacterial agents, LpxC inhibitors would not only have to inhibit the enzymatic activity of LpxC from a variety of bacteria, but would have to defeat the intrinsic resistance mechanisms of gram-negative bacteria, as described

above: they would have to penetrate the outer membrane and be relatively unsusceptible to multidrug efflux pumps.

**[0007]** Researchers have identified a few compounds with antibacterial activity that target lipid A biosynthesis. WO 97/42179 to Patchett et al. discloses compounds of the formula:

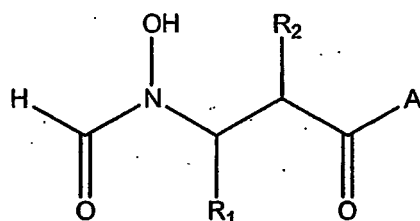


**[0008]** The compounds possess activity against certain gram-negative organisms, for example *Escherichia coli*, but are not active against other medically important gram-negative bacteria, for example *Pseudomonas aeruginosa*. Subsequent studies have found that the primary reason for their inactivity against particular, medically important gram-negative bacteria is their poor ability to inhibit *P. aeruginosa* LpxC; efflux by the major multidrug efflux pump or inability to penetrate the outer membrane were not the critical factors.

**[0009]** Jackman et al., in *J. Biol. Chem.* (vol. 275, no. 15, April 14, 2000, pps. 11002-11009), discuss the mechanism of lipid A biosynthesis in the context of gram-negative bacteria and discloses a new class of hydroxamate-containing inhibitors of LpxC. Wyckoff et al., in *Trends in Microbiology* (vol. 6, no. 4, April 1998, pps. 154-159), discuss the role of LpxC in lipid A biosynthesis and its role in regulation. Wyckoff et al. disclose a few oxazoline hydroxamic acids that inhibit bacterial growth. However, Wyckoff et al. also discuss the shortcomings of the available deacetylase inhibitors as bactericidal agents against *Pseudomonas* and that more work is needed to be done in the area.

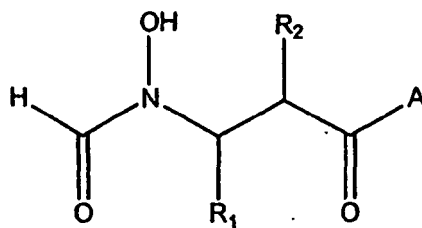
**[0010]** Thus, an increasing need exists for LpxC inhibitors that have activity as bactericidal agents against gram-negative bacteria. It is, accordingly, an object of this invention to provide compounds and combinations of such compounds for use in the preparation of antibacterials and other pharmaceuticals capable of inhibiting Gram-negative bacterial infections.

**[0011]** U.S. Patent Publication No. 2001/0053555 (U.S. Patent Application Serial No. 08/958,638) published December 20, 2001, corresponding to WO 98/18754 published May 7, 1998 discloses a combinatorial library of hydroxylamine, hydroxamic acid, hydroxyurea and hydroxylsulfonamide compounds purported to be potentially useful as inhibitors of metalloproteases. U.S. Patent No. 6,281,245, a continuation in part of U.S. 08/958,638 claims a method of inhibiting a deformylase enzyme by administering one of the hydroxylamine compounds from the combinatorial library as disclosed in U.S. Patent Publication No. 2001/0053555 and the corresponding WO 98/18754. Related to the above disclosed patent publications is WO 99/57097, published November 11, 1999, that discloses a method of solid phase synthesis of the hydroxylamine library of compounds. WO 00/61134 (to British Biotech Pharmaceuticals Limited), published October 19, 2000, discloses compounds of the formula below:



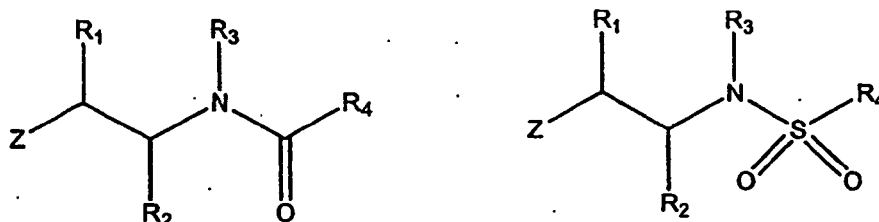
**[0012]** The compounds are useful as antimicrobial agents that are believed to have bactericidal activity at least in part to intracellular inhibition of bacterial polypeptide deformylase.

**[0013]** In an earlier to British Biotech Pharmaceuticals Limited, WO 99/39704, published August 12, 1999, compounds of the formula below are disclosed:



[0014] The compounds are useful as antimicrobial agents useful against gram-negative and gram positive bacteria.

[0015] Recently, De Novo Pharmaceuticals LTD disclosed in WO 02/50081, published June 27, 2002, antibacterial and antiprotozoal agents having the formulae shown below:

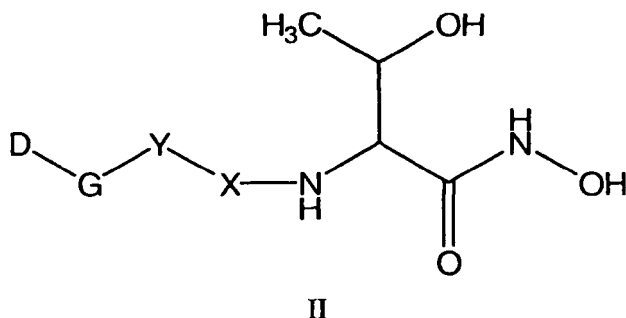


[0016] The patent publication discusses that the antibacterial activity is due, at least in part, to intracellular inhibition of bacterial polypeptide deformylase.

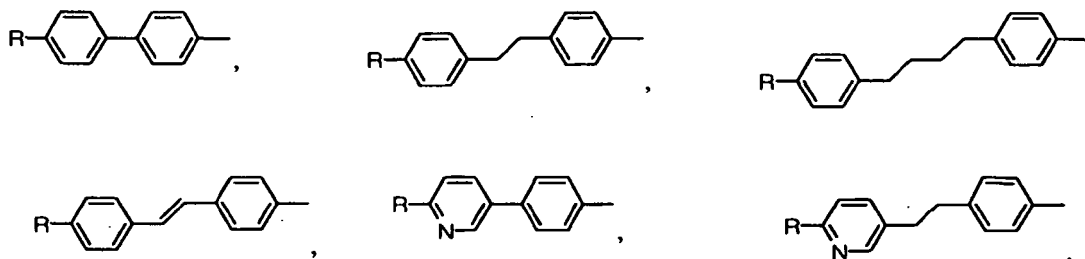
## SUMMARY OF THE INVENTION

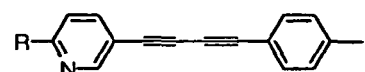
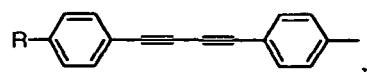
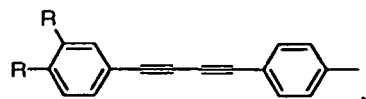
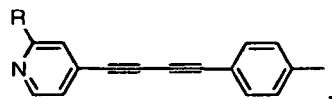
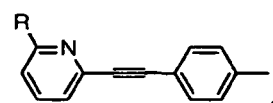
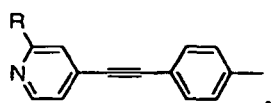
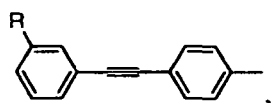
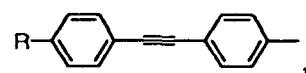
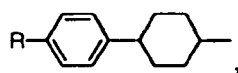
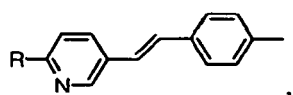
[0017] The present invention provides novel compounds, pharmaceutical formulations including the compounds, compounds for use in methods of inhibiting UDP-3-O-(R 3-hydroxydecanoyl)-N-acetylglucosamine deacetylase (LpxC), and compounds for use in methods of treating gram-negative bacterial infections.

[0018] In one embodiment, the present invention provides compounds of formula II:



or a stereoisomer, pharmaceutically acceptable salt, or ester thereof, wherein D-G-Y taken together, is selected from the group consisting of

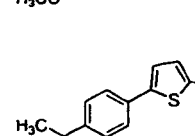
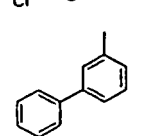
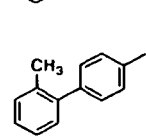
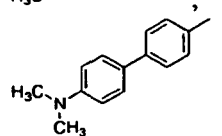
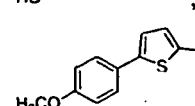
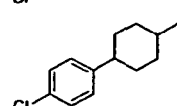
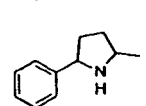
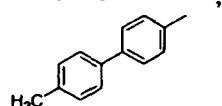
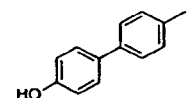
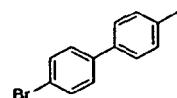
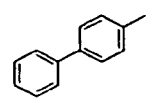
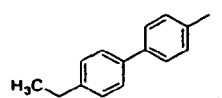


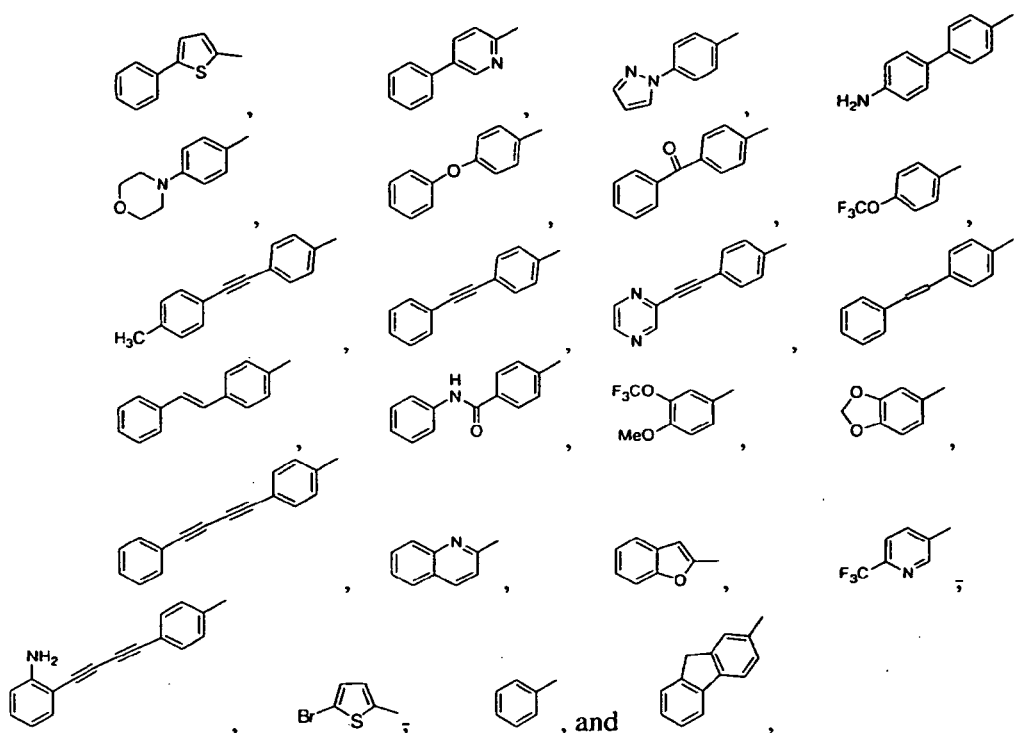


and



or





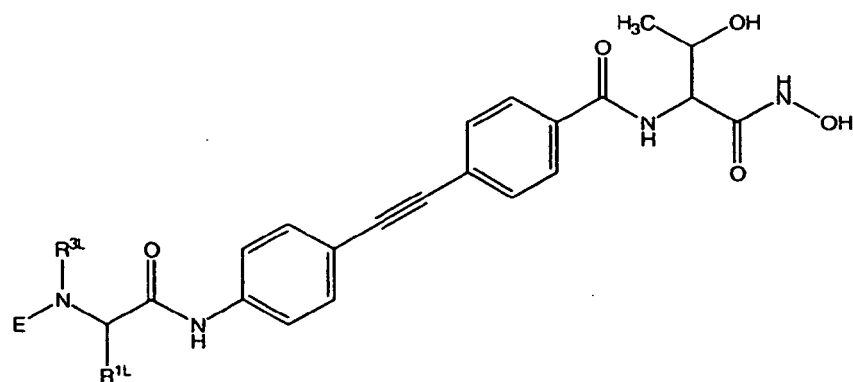
wherein

R is selected from the group consisting of -CH<sub>3</sub>, -C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>OH, -OH, -OCH<sub>3</sub>, -OC<sub>2</sub>H<sub>5</sub>, -OCF<sub>3</sub>, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>H, -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, -NH<sub>2</sub>, -F, -Cl, -Br, -CF<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -NHSO<sub>2</sub>CH<sub>3</sub>, and -NHCOCH<sub>3</sub>; and

X is selected from the groups consisting of

- (1) -(C=O)-,
- (2) -C<sub>1</sub>-C<sub>6</sub>-alkyl-(C=O)-, and
- (3) -C<sub>2</sub>-C<sub>6</sub>-alkenyl-(C=O)-.

**[0019]** In another embodiment, the present invention provides a compound having the formula VI:



VI

or a stereoisomer, pharmaceutically acceptable salt, or ester thereof, wherein E is absent or selected from the group consisting of

- (1) H,
- (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
- (3) substituted or unsubstituted aryl,
- (4) substituted or unsubstituted heterocyclyl, and

(5) substituted or unsubstituted heteroaryl,

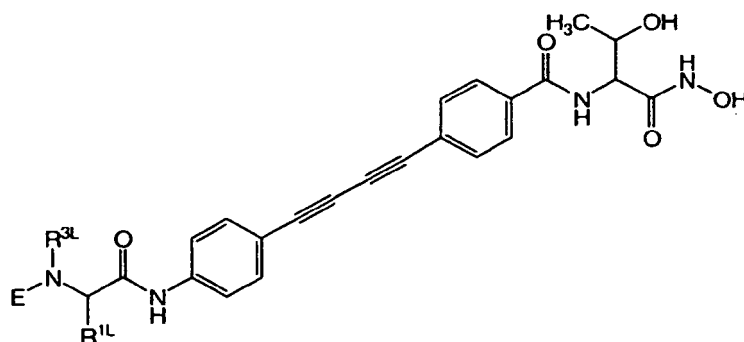
or E and R<sup>3L</sup>, together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 10 ring atoms, wherein 1-4 ring atoms of the heterocyclic ring system are selected from N, O and S;

R<sup>1L</sup>, R<sup>3L</sup> are independently selected from the group consisting of

- (1) H,
- (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
- (3) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with aryl,
- (4) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heterocyclyl, and
- (5) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heteroaryl,

or R<sup>1L</sup> and R<sup>3L</sup>, together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S.

**[0020]** In a further embodiment, the invention provides a compound having the formula VIII:



VIII

or a stereoisomer, pharmaceutically acceptable salt, or ester, wherein E is absent or selected from the group consisting of

- (1) H,
- (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
- (3) substituted or unsubstituted aryl,
- (4) substituted or unsubstituted heterocyclyl, and
- (5) substituted or unsubstituted heteroaryl,

or E and R<sup>3L</sup>, together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 10 ring atoms, wherein 1-4 ring atoms of the heterocyclic ring system are selected from N, O and S;

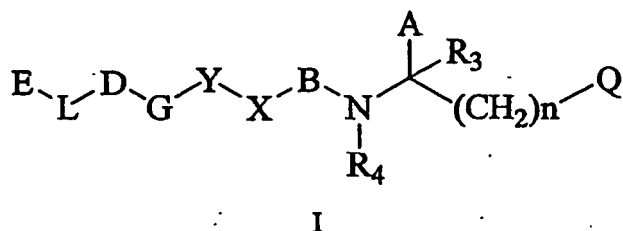
R<sup>1L</sup>, R<sup>3L</sup> are independently selected from the group consisting of

- (1) H,
- (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
- (3) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with aryl,
- (4) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heterocyclyl, and
- (5) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heteroaryl,

or R<sup>1L</sup> and R<sup>3L</sup>, together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S.

**[0021]** The present disclosure provides compounds of formula I:





or stereoisomers, pharmaceutically acceptable salts, esters, and prodrugs thereof, wherein E is absent or selected from the group consisting of

- (1) H,
- (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
- (3) substituted or unsubstituted C<sub>2</sub>-C<sub>6</sub>-alkenyl,
- (4) substituted or unsubstituted C<sub>2</sub>-C<sub>6</sub>-alkynyl,
- (5) substituted or unsubstituted aryl,
- (6) substituted or unsubstituted heterocyclyl, and
- (7) substituted or unsubstituted heteroaryl;

L is absent or selected from the group consisting of

- (1) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
  - (2) -(NH)<sub>0-1</sub>-(CH<sub>2</sub>)<sub>j</sub>-NR<sup>3L</sup>-(CH<sub>2</sub>)<sub>k</sub>-,
  - (3) -(NH)<sub>0-1</sub>C(R<sup>1L</sup>, R<sup>2L</sup>)-NR<sup>3L</sup>-C(R<sup>1L</sup>, R<sup>2L</sup>)-,
  - (4) -C(R<sup>1L</sup>, R<sup>2L</sup>)-O-C(R<sup>1L</sup>, R<sup>2L</sup>)-,
  - (5) -(CH<sub>2</sub>)<sub>j</sub>-NR<sup>3L</sup>-C(R<sup>1L</sup>, R<sup>2L</sup>)-CONH-(CH<sub>2</sub>)<sub>k</sub>-,
  - (6) -CO-C(R<sup>1L</sup>, R<sup>2L</sup>)-NHCO-,
  - (7) -CONH-,
  - (8) -NHCO-,
- wherein
- R<sup>1L</sup>, R<sup>2L</sup>, and R<sup>3L</sup> are independently selected from the group consisting of

- (a) H,
- (b) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
- (c) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with aryl,
- (d) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heterocyclyl, and
- (e) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heteroaryl,

or R<sup>1L</sup> and R<sup>3L</sup>, together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S;

j is an integer of 0-4;

k is an integer of 0-4;

D is absent or selected from the group consisting of

- (1) substituted or unsubstituted C<sub>3</sub>-C<sub>8</sub>-cycloalkyl,
- (2) substituted or unsubstituted aryl,
- (3) substituted or unsubstituted heterocyclyl, and
- (4) substituted or unsubstituted heteroaryl;

G is absent or selected from the group consisting of

- (1) -(CH<sub>2</sub>)<sub>i</sub>-O-(CH<sub>2</sub>)<sub>i</sub>-,
- (2) -(CH<sub>2</sub>)<sub>i</sub>-S-(CH<sub>2</sub>)<sub>i</sub>-,
- (3) -(CH<sub>2</sub>)<sub>i</sub>-NR<sup>g</sup>-(CH<sub>2</sub>)<sub>i</sub>-,

- (4)  $-\text{C}(=\text{O})-$ ,  
 (5)  $-\text{NHC}(=\text{O})-$ ,  
 (6)  $-\text{C}(=\text{O})\text{NH}-$ ,  
 (7)  $-(\text{CH}_2)_i\text{NHCH}_2\text{C}(=\text{O})\text{NH}-$ ,  
 (8)  $-\text{C}\equiv\text{C}-$ ,  
 (9)  $-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-$ , and  
 (10)  $-\text{C}=\text{C}-$ ;

wherein

R<sub>g</sub> is H or substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl; i is an integer of 0-4;

Y is selected from the group consisting of

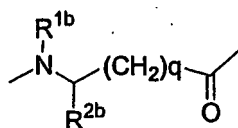
- (1) substituted or unsubstituted C<sub>3</sub>-C<sub>8</sub>-cycloalkyl,  
 (2) substituted or unsubstituted aryl,  
 (3) substituted or unsubstituted heterocyclyl, and  
 (4) substituted or unsubstituted heteroaryl;

X is selected from the group consisting of

- (1)  $-\text{C}(=\text{O})$ ,  
 (2)  $-\text{C}_1-\text{C}_6\text{-alkyl}-\text{C}(=\text{O})-$ ,  
 (3)  $-\text{C}_2-\text{C}_6\text{-alkenyl}-\text{C}(=\text{O})-$ ,  
 (4)  $-\text{C}_2-\text{C}_6\text{-alkynyl}-\text{C}(=\text{O})-$ , and  
 (5)  $-\text{CH}_2-$ ;

or when B is absent, X and A, together with the atoms to which they are attached can form a heterocyclic ring, having from 5 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S;

B is absent or



wherein R<sup>1b</sup> and R<sup>2b</sup>, are independently selected from the group consisting of

- (a) H,  
 (b) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,  
 (c) substituted or unsubstituted C<sub>2</sub>-C<sub>6</sub>-alkenyl,  
 (d) substituted or unsubstituted C<sub>2</sub>-C<sub>6</sub>-alkynyl,  
 (e) substituted or unsubstituted aryl,  
 (f) substituted or unsubstituted heterocyclyl,  
 (g) substituted or unsubstituted heteroaryl,  
 (h) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with aryl,  
 (i) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heterocyclyl, and  
 (j) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heteroaryl,

or R<sup>1b</sup> and R<sup>2b</sup>, together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 5 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S;  
 q is an integer of 0-4;

R<sub>3</sub> is H or substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,

or R<sub>3</sub> and A, together with the atoms to which they are attached can form a substituted or unsubstituted 3-10 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S;

R<sub>4</sub> is H or substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,

or R<sub>4</sub> and A, together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S;

n is an integer of 0-6;

A is selected from the group consisting of

- (1) H,
- (2)  $-(CH_2)_rC(R^{1a}, R^{2a})(CH_2)_sOR^{3a}$ ,
- (3)  $-(CH_2)_rC(R^{1a}, R^{2a})N(R^{4a}, R^{5a})$ ,
- (4)  $-(CH_2)_rC(R^{1a}, R^{2a})N(R^{4a})COR^{3a}$ ,
- (5)  $-(CH_2)_rC(R^{1a}, R^{2a})NHCON(R^{4a}, R^{5a})$ ,
- (6)  $-(CH_2)_rC(R^{1a}, R^{2a})NHC(=NH)N(R^{4a}, R^{5a})$ ,
- (7)  $-CH(R^{1a}, R^{2a})$ ,
- (8)  $-C\equiv CH$ ,
- (9)  $-(CH_2)_rC(R^{1a}, R^{2a})CN$ ,
- (10)  $-(CH_2)_rC(R^{1a}, R^{2a})CO_2R^{3a}$ , and
- (11)  $-(CH_2)_rC(R^{1a}, R^{2a})CON(R^{4a}, R^{5a})$ ,

wherein  $R^{1a}$ ,  $R^{2a}$ ,  $R^{3a}$ ,  $R^{4a}$ , and  $R^{5a}$  are independently selected from the group consisting of

- (a) H,
- (b) substituted or unsubstituted  $C_1$ - $C_6$ -alkyl,
- (c) substituted or unsubstituted aryl,
- (d) substituted or unsubstituted heterocyclyl,
- (e) substituted or unsubstituted heteroaryl,
- (f)  $C_1$ - $C_6$ -alkyl substituted with aryl,
- (g)  $C_1$ - $C_6$ -alkyl substituted with heterocyclyl, and
- (h)  $C_1$ - $C_6$ -alkyl substituted with heteroaryl,

or  $R^{4a}$  and  $R^{5a}$  together with the N atom to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 5 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S;

r is an integer of 0-4;

s is an integer of 0-4;

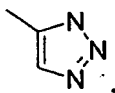
Q is absent or selected from the group consisting of

- (1)  $-C(=O)N(R_1, R_2)$ ,
- (2)  $-NHC(=O)N(R_1, R_2)$ ,
- (3)  $-N(OH)C(=O)N(R_1, R_2)$ ,
- (4)  $-CH(OH)C(=O)N(R_1, R_2)$ ,
- (5)  $-CH[N(R^{2q}, R^{3q})]C(=O)N(R_1, R_2)$ ,
- (6)  $-CHR_{1q}C(=O)N(R_1, R_2)$ ,
- (7)  $-CO_2H$ ,
- (8)  $-C(=O)NHSO_2R^{4q}$ ,
- (9)  $-SO_2NH_2$ ,
- (10)  $N(OH)C(=O)R^{1q}$ ,
- (11)  $-N(OH)SO_2R^{4q}$ ,
- (12)  $-NHSO_2R^{4q}$ ,
- (13)  $-SH$ ,
- (14)  $-CH(SH)(CH_2)_{0-1}C(=O)N(R_1, R_2)$ ,
- (15)  $-CH(SH)(CH_2)_{0-1}CO_2H$ ,
- (16)  $-CH(OH)(CH_2)_{0-1}CO_2H$ ,
- (17)  $-CH(SH)CH_2CO_2R^{1q}$ ,
- (18)  $-CH(OH)(CH_2)SO_2NH_2$ ,
- (19)  $-CH(CH_2SH)NHCOR^{1q}$ ,
- (20)  $-CH(CH_2SH)NHSO_2R^{4q}$ ,
- (21)  $-CH(CH_2SR^{5q})CO_2H$ ,
- (22)  $-CH(CH_2SH)NHSO_2NH_2$ ,
- (23)  $-CH(CH_2OH)CO_2H$ ,
- (24)  $-CH(CH_2OH)NHSO_2NH_2$ ,
- (25)  $-C(=O)CH_2CO_2H$ ,

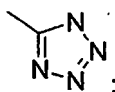
- (26)  $-\text{C}(=\text{O})(\text{CH}_2)_{0-1}\text{CONH}_2$ ,  
 (27)  $-\text{OSO}_2\text{NHR}^{5q}$ ,  
 (28)  $-\text{SO}_2\text{NHNH}_2$ ,  
 (29)  $-\text{P}(=\text{O})(\text{OH})_2$ ,  
 (30)



(31)



and  
 (32)



wherein

$R_1$  is selected from the group consisting of

- (1) H,  
 (2)  $-\text{OH}$ ,  
 (3)  $-\text{OC}_{1-6}\text{-alkyl}$ ,  
 (4)  $\text{N}(\text{R}^{2q}, \text{R}^{3q})$ , and  
 (5) substituted or unsubstituted  $\text{C}_{1-6}\text{-alkyl}$ ;

$R_2$  is selected from the group consisting of

- (1) H,  
 (2) substituted or unsubstituted  $\text{C}_1\text{-C}_6\text{-alkyl}$ ,  
 (3) substituted or unsubstituted  $\text{C}_2\text{-C}_6\text{-alkenyl}$ ,  
 (4) substituted or unsubstituted  $\text{C}_2\text{-C}_6\text{-alkenyl}$ ,  
 (5) substituted or unsubstituted aryl,  
 (6) substituted or unsubstituted heterocyclyl,  
 (7) substituted or unsubstituted heteroaryl,  
 (8)  $\text{C}_1\text{-C}_6\text{-alkyl}$  substituted with aryl,  
 (9)  $\text{C}_1\text{-C}_6\text{-alkyl}$  substituted with heterocyclyl, and  
 (10)  $\text{C}_1\text{-C}_6\text{-alkyl}$  substituted with heteroaryl,

or  $R^1$  and  $R^2$ , together with the N atom to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 10 ring atoms, wherein 1-4 ring atoms of the heterocyclic ring system are selected from N, O and S;  
 or  $R^2$  and  $R^4$ , together with the N atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 10 ring atoms, wherein 1-4 ring atoms of the heterocyclic ring system are selected from N, O and S;  
 $R^{1q}$ ,  $R^{2q}$ ,  $R^{3q}$ ,  $R^{4q}$ , and  $R^{5q}$  are selected from H or  $\text{C}_1\text{-C}_6\text{-alkyl}$ ,  
 wherein B is absent, or E, L, G, and B are absent, or E, L, and G are absent, or E, L, and B are absent, or B, L, D, G, and B are absent.

**[0022]** In one aspect, the disclosure provides a method of inhibiting a deacetylase enzyme in a gram-negative bacteria, thereby affecting bacterial growth, comprising administering to a patient in need of such inhibition a compound of formula I.

**[0023]** In another aspect, the disclosure provides a method of inhibiting LpxC, thereby modulating the virulence of a bacterial infection, comprising administering to a patient in need of such inhibition a compound of formula I.

**[0024]** In another aspect; the disclosure provides a method for treating a subject with a gram-negative bacterial infection comprising administering to the subject in need thereof an antibacterially effective amount of a compound of formula I with a pharmaceutically acceptable carrier. In a preferred embodiment of the method of treatment, the subject is a mammal and in some embodiments, a human.

**[0025]** In another aspect, the disclosure provides a method of administering an inhibitory amount of a compound of formula I to fermentative or non-fermentative gram-negative bacteria. In a preferred embodiment of the method of administering an inhibitory amount of a compound of formula I to fermentative or non-fermentative gram-negative bacteria, the gram-negative bacteria are selected from the group consisting of *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *Alcaligenes xylosoxidans*, *Acinetobacter*, *Enterobacteriaceae*, *Haemophilus*, and *Neisseria* species.

**[0026]** In another aspect, the disclosure provides a method of administering an inhibitory amount of a compound of formula I to gram-negative bacteria, such as *Enterobacteriaceae* which is selected from the group consisting of organisms such as *Serratia*, *Proteus*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Providencia*, *Morganella*, *Cedecea*, and *Edwardsiella* species and *Escherichia coli*.

**[0027]** Another aspect of the disclosure provides a pharmaceutical composition comprising an effective amount of a compound of Formula I with a pharmaceutically acceptable carrier thereof.

**[0028]** Pharmaceutical formulations according to the present disclosure are provided which include any of the compounds described above in combination with a pharmaceutically acceptable carrier.

**[0029]** Another aspect of the disclosure provides a method of co-administering the compound of formula I with other therapeutic agents that are selected for their particular usefulness against the condition that is being treated.

**[0030]** For example, the compound of formula I is useful in combination with other anti-bacterial agents. The compound of formula I augments the sensitivity of gram-negative bacteria to existing classes of antibacterials. Combinations of the presently disclosed compounds as specified in the claims with other anti-bacterial agents are within the scope of the invention. Such anti-bacterial agents include erythromycin, rifampicin, Nalidixic acid, carbenicillin, bacitracin, cycloserine, fosfomycin, and vancomycin.

## DETAILED DESCRIPTION

**[0031]** The present invention provides novel compounds as specified in the claims, for use in methods for inhibiting LpxC in gram-negative bacteria, and novel compounds for use in methods for treating bacterial infections. The compounds provided herein can be formulated into pharmaceutical formulations and medicaments that are useful in the methods of the disclosure. The invention also provides for the use of the compounds in preparing medicaments and pharmaceutical formulations, for compounds for use in inhibiting LpxC, and compounds for use in treating bacterial infections in a subject.

**[0032]** The following abbreviations and definitions are used throughout this application:

**[0033]** "LpxC" is an abbreviation that stands for UDP-3-O-(R-3-hydroxydecanoyl)-N-acetylglucosamine deacetylase.

**[0034]** Generally, reference to a certain element such as hydrogen or H is meant to include all isotopes of that element. For example, if an R group is defined to include hydrogen or H, it also includes deuterium and tritium.

**[0035]** The phrase "alkyl" refers to alkyl groups that do not contain heteroatoms. Thus the phrase includes straight chain alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl.

The phrase also includes branched chain isomers of straight chain alkyl groups, including the following that are provided by way of example: -CH(CH<sub>3</sub>)<sub>2</sub>, -CH(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>3</sub>), -CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -C(CH<sub>3</sub>)<sub>3</sub>, -C(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>, -CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>CH(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>3</sub>), -CH<sub>2</sub>CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>, -CH<sub>2</sub>C(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>, -CH(CH<sub>3</sub>)CH(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>3</sub>), -CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>3</sub>), -CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>CH<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>C(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>, -CH(CH<sub>3</sub>)CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, -CH(CH<sub>3</sub>)CH(CH<sub>3</sub>)CH(CH<sub>3</sub>)<sub>2</sub> and -CH(CH<sub>2</sub>CH<sub>3</sub>)CH(CH<sub>3</sub>)CH(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>3</sub>). The phrase also includes cyclic alkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl and such rings substituted with straight and branched chain alkyl groups as defined above. Thus the phrase alkyl groups includes primary alkyl groups, secondary alkyl groups, and tertiary alkyl groups. Preferred alkyl groups include straight and branched chain alkyl groups and cyclic alkyl groups having 1 to 12 carbon atoms.

**[0036]** The phrase "substituted alkyl" refers to an alkyl group as defined above in which one or more bonds to a carbon(s) or hydrogen(s) are replaced by a bond to non-hydrogen and non-carbon atoms such as a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, aryloxy groups, and ester groups; a sulfur atom in groups such as thiol groups, alkyl and aryl sulfide groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as in trialkylsilyl groups, dialkylarylsilyl groups, alkylarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. Substituted alkyl groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom is replaced by a higher-order bond (e.g., a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; nitrogen in groups such as imines, oximes, hydrazones, and nitriles. Substituted alkyl groups further include alkyl groups

in which one or more bonds to a carbon(s) or hydrogen(s) atoms is replaced by a bond to an aryl, heterocyclyl group, or cycloalkyl group. Preferred substituted alkyl groups include, among others, alkyl groups in which one or more bonds to a carbon or hydrogen atom is/are replaced by one or more bonds to fluorine atoms. Another preferred substituted alkyl group is the trifluoromethyl group and other alkyl groups that contain the trifluoromethyl group. Other preferred substituted alkyl groups include those in which one or more bonds to a carbon or hydrogen atom is replaced by a bond to an oxygen atom such that the substituted alkyl group contains a hydroxyl, alkoxy, or aryloxy group. Still other preferred substituted alkyl groups include alkyl groups that have an amine, or a substituted or unsubstituted alkylamine, dialkylamine, arylamine, (alkyl)(aryl)amine, diarylamine, heterocyclylamine, diheterocyclylamine, (alkyl)(heterocyclyl)amine, or (aryl)(heterocyclyl)amine group.

**[0037]** The phrase "alkenyl" refers to straight and branched chain and cyclic groups such as those described with respect to alkyl groups as defined above, except that at least one double bond exists between two carbon atoms. Examples include vinyl,  $-\text{CH}=\text{C}(\text{H})(\text{CH}_3)$ ,  $-\text{CH}=\text{C}(\text{CH}_3)_2$ ,  $-\text{C}(\text{CH}_3)=\text{C}(\text{H})_2$ ,  $-\text{C}(\text{CH}_3)=\text{C}(\text{H})(\text{CH}_3)$ ,  $-\text{C}(\text{CH}_2\text{CH}_3)=\text{CH}_2$ , cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, and hexadienyl among others. The phrase "substituted alkenyl" has the same meaning with respect to alkenyl groups that substituted alkyl groups had with respect to unsubstituted alkyl groups. A substituted alkenyl group includes alkenyl groups in which a non-carbon or non-hydrogen atom is bonded to a carbon double bonded to another carbon and those in which one of the non-carbon or non-hydrogen atoms is bonded to a carbon not involved in a double bond to another carbon.

**[0038]** The phrase "alkynyl" refers to straight and branched chain groups such as those described with respect to alkyl groups as defined above, except that at least one triple bond exists between two carbon atoms. Examples include  $-\text{C}\equiv\text{C}(\text{H})$ ,  $-\text{C}\equiv\text{C}(\text{CH}_3)$ ,  $-\text{C}\equiv\text{C}(\text{CH}_2\text{CH}_3)$ ,  $-\text{C}(\text{H}_2)\text{C}\equiv\text{C}(\text{H})$ ,  $-\text{C}(\text{H}_2)\text{C}\equiv\text{C}(\text{CH}_3)$ , and  $-\text{C}(\text{H})_2\text{C}\equiv\text{C}(\text{CH}_2\text{CH}_3)$  among others. The phrase "substituted alkynyl" has the same meaning with respect to alkynyl groups that substituted alkyl groups had with respect to unsubstituted alkyl groups. A substituted alkynyl group includes alkynyl groups in which a non-carbon or non-hydrogen atom is bonded to a carbon triple bonded to another carbon and those in which a non-carbon or non-hydrogen atom is bonded to a carbon not involved in a triple bond to another carbon.

**[0039]** The phrase "heterocyclyl" refers to both aromatic and nonaromatic ring compounds including monocyclic, bicyclic, and polycyclic ring compounds such as quinuclidinyl, containing 3 or more ring members of which one or more is a heteroatom such as N, O, and S. Although the phrase "unsubstituted heterocyclyl" includes condensed heterocyclic rings such as benzimidazolyl, it does not include heterocyclyl groups that have other groups such as alkyl or halo groups bonded to one of the ring members as compounds such as 2-methylbenzimidazolyl are substituted heterocyclyl groups. Examples of heterocyclyl groups include unsaturated 3 to 8 membered rings containing 1 to 4 nitrogen atoms such as pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl etc.), tetrazolyl, (e.g. 1H-tetrazolyl, 2H tetrazolyl, etc.); saturated 3 to 8 membered rings containing 1 to 4 nitrogen atoms such as, but not limited to, pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl; condensed unsaturated heterocyclic groups containing 1 to 4 nitrogen atoms such as indolyl, isoindolyl, indolinyl, indoliziny, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl; unsaturated 3 to 8 membered rings containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms such as oxazolyl, isoxazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl); saturated 3 to 8 membered rings containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms such as morpholinyl; unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, benzoxazolyl, benzoxadiazolyl, benzoxazinyl (e.g. 2H-1,4-benzoxazinyl etc.); unsaturated 3 to 8 membered rings containing 1 to 3 sulfur atoms and 1 to 3 nitrogen atoms such as thiazolyl, isothiazolyl, thiadiazolyl (e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.); saturated 3 to 8 membered rings containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms such as thiazolidinyl; saturated and unsaturated 3 to 8 membered rings containing 1 to 2 sulfur atoms such as thienyl, dihydrodithiyl, dihydrodithionyl, tetrahydrothiophene, tetrahydrothiopyran; unsaturated condensed heterocyclic rings containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms such as benzothiazolyl, benzothiadiazolyl, benzothiazinyl (e.g. 2H-1,4-benzothiazinyl, etc.), dihydrobenzothiazinyl (e.g. 2H-3,4-dihydrobenzothiazinyl, etc.), unsaturated 3 to 8 membered rings containing oxygen atoms such as furyl; unsaturated condensed heterocyclic rings containing 1 to 2 oxygen atoms such as benzodioxolyl (e.g. 1,3-benzodioxolyl, etc.); unsaturated 3 to 8 membered rings containing an oxygen atom and 1 to 2 sulfur atoms such as dihydrooxathiinyl; saturated 3 to 8 membered rings containing 1 to 2 oxygen atoms and 1 to 2 sulfur atoms such as 1,4-oxathiane; unsaturated condensed rings containing 1 to 2 sulfur atoms such as benzothienyl, benzodithiyl; and unsaturated condensed heterocyclic rings containing an oxygen atom and 1 to 2 oxygen atoms such as benzoxathiinyl. Heterocyclyl group also include those described above in which one or more S atoms in the ring is double-bonded to one or two oxygen atoms (sulfoxides and sulfones). For example, heterocyclyl groups include tetrahydrothiophene, tetrahydrothiophene oxide, and tetrahydrothiophene 1,1-dioxide. Preferred heterocyclyl groups contain 5 or 6 ring members. More preferred heterocyclyl groups include morpholine, piperazine, piperidine, pyrrolidine, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, thiomorpholine, thiomorpholine in which the S atom of the thiomorpholine is bonded to one or more O atoms, pyrrole, homopiperazine, oxazolidin-2-one, pyrrolidin-2-one, oxazole, quinuclidine, thiazole, isoxazole, furan, and tetrahydrofuran.

**[0040]** The phrase "substituted heterocyclyl" refers to a heterocyclyl group as defined above in which one of the ring members is bonded to a non-hydrogen atom such as described above with respect to substituted alkyl groups and substituted aryl groups. Examples, include 2-methylbenzimidazolyl, 5-methylbenzimidazolyl, 5-chlorobenzthiazolyl, 1-methyl piperazinyl, and 2-chloropyridyl.

**[0041]** The phrase "aryl" refers to aryl groups that do not contain heteroatoms. Thus the phrase includes groups such as phenyl, biphenyl, anthracenyl, naphthenyl by way of example. Although the phrase "unsubstituted aryl" includes groups containing condensed rings such as naphthalene, it does not include aryl groups that have other groups such as alkyl or halo groups bonded to one of the ring members, as aryl groups such as tolyl are considered herein to be substituted aryl groups as described below. A preferred unsubstituted aryl group is phenyl. Unsubstituted aryl groups may be bonded to one or more carbon atom(s), oxygen atom(s), nitrogen atom(s), and/or sulfur atom(s) in the parent compound, however.

**[0042]** The phrase "substituted aryl group" has the same meaning with respect to unsubstituted aryl groups that substituted alkyl groups had with respect to unsubstituted alkyl groups. However, a substituted aryl group also includes aryl groups in which one of the aromatic carbons is bonded to one of the non-carbon or non-hydrogen atoms described above and also includes aryl groups in which one or more aromatic carbons of the aryl group is bonded to a substituted and/or unsubstituted alkyl, alkenyl, or alkynyl group as defined herein. This includes bonding arrangements in which two carbon atoms of an aryl group are bonded to two atoms of an alkyl, alkenyl, or alkynyl group to define a fused ring system (e.g. dihydronaphthyl or tetrahydronaphthyl). Thus, the phrase "substituted aryl" includes, tolyl, and hydroxyphenyl among others. Preferred substituents include straight and branched chain alkyl groups, -CH<sub>3</sub>, -C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>OH, -OH, -OCH<sub>3</sub>, -OC<sub>2</sub>H<sub>5</sub>, -OCF<sub>3</sub>, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>H, -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, -NH<sub>2</sub>, -F, -Cl, Br, -CF<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -NHSO<sub>2</sub>CH<sub>3</sub>, -NHCOCH<sub>3</sub>. The term "heteroaryl", as used herein, refers to a cyclic or bicyclic aromatic radical having from five to ten ring atoms in each ring of which one atom of the cyclic or bicyclic ring is selected from S, O and N; zero, one or two ring atoms are additional heteroatoms independently selected from S, O and N; and the remaining ring atoms are carbon, the radical being joined to the rest of the molecule via any of the ring atoms, such as, for example, pyridyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, and naphthyridinyl.

**[0043]** The term "substituted heteroaryl" as used herein refers to a heteroaryl group as defined herein substituted by independent replacement of one, two or three of the hydrogen atoms thereon with Cl, Br, F, I, OH, CN, C<sub>1</sub>-C<sub>3</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>1</sub>-C<sub>6</sub>-alkoxy substituted with aryl, haloalkyl, thioalkoxy, amino, alkylamino, dialkylamino, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide. In addition, any one substituent may be an aryl, heteroaryl, or heterocycloalkyl group. Preferred substituents include straight and branched chain alkyl groups, -CH<sub>3</sub>, -C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>OH, -OH, -OCH<sub>3</sub>, -OC<sub>2</sub>H<sub>5</sub>, -OCF<sub>3</sub>, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>H, -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, -NH<sub>2</sub>, -F, -Cl, Br, -CF<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -NHSO<sub>2</sub>CH<sub>3</sub>, NHCOCH<sub>3</sub>.

**[0044]** The term "biaryl" refers to a group or substituent to which two aryl groups, which are not condensed to each other, are bound. Exemplary biaryl compounds include, for example, phenylbenzene, diphenyldiazene, 4-methylthio-1-phenylbenzene, phenoxybenzene, (2-phenylethynyl)benzene, diphenyl ketone, (4-phenylbuta-1,3-diynyl)benzene, phenylbenzylamine, (phenylmethoxy)benzene, and the like. Preferred optionally substituted biaryl groups include: 2-(phenylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 1,4-diphenylbenzene, N-[4-(2-phenylethynyl)phenyl]-2-[benzylamino]acetamide, 2-amino-N-[4-(2-phenylethynyl)phenyl]propanamide, 2-amino-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-(cyclopropylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-(ethylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-[(2-methylpropyl)amino]-N-[4-(2-phenylethynyl)phenyl]acetamide, 5-phenyl-2H-benzo[d][1,3]dioxolene, 2-chloro-1-methoxy-4-phenylbenzene, 2-[(imidazolylmethyl)amino]-N-[4-(2-phenylethynyl)phenyl]acetamide, 4-phenyl-1-phenoxybenzene, N-(2-aminoethyl)[4-(2-phenylethynyl)phenyl]carboxamide, 2-[[4-(4-fluorophenyl)methyl]amino]-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-[[4-(4-methylphenyl)methyl]amino]-N-[4-(2-phenylethynyl)phenyl]acetamide, 4-phenyl-1-(trifluoromethyl)benzene, 1-butyl-4-phenylbenzene, 2-(cyclohexylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-(ethylmethylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-(butylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, N-[4-(2-phenylethynyl)phenyl]-2-(4-pyridylamino)acetamide, N-[4-(2-phenylethynyl)phenyl]-2-(quinuclidin-3-ylamino)acetamide, N-[4-(2-phenylethynyl)phenyl]pyrrolidin-2-ylcarboxamide, 2-amino-3-methyl-N-[4-(2-phenylethynyl)phenyl]butanamide, 4-(4-phenylbuta-1,3-diynyl)phenylamine, 2-(dimethylamino)-N-[4-(4-phenylbuta-1,3-diynyl)phenyl]acetamide, 2-(ethylamino)-N-[4-(4-phenylbuta-1,3-diynyl)phenyl]acetamide, 4-ethyl-1-phenylbenzene, 1-[4-(2-phenylethynyl)phenyl]ethan-1-one, N-(1-carbamoyl-2-hydroxypropyl)[4-(4-phenylbuta-1,3-diynyl)phenyl]carboxamide, N-[4-(2-phenylethynyl)phenyl]propanamide, 4-methoxyphenyl phenyl ketone, phenyl-N-benzamide, (tert-butoxy)-N-[(4-phenylphenyl)methyl]carboxamide, 2-(3-phenylphenoxy)ethanehydroxamic acid, 3-phenylphenyl propanoate, 1-(4-ethoxyphenyl)-4-methoxybenzene, and [4-(2-phenylethynyl)phenyl]pyrrole.

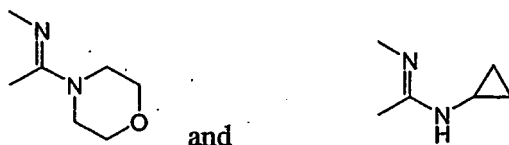
**[0045]** The term "heteroarylaryl" refers to a biaryl group where one of the aryl groups is a heteroaryl group. Exemplary heteroarylaryl groups include, for example, 2-phenylpyridine, phenylpyrrole, 3-(2-phenylethynyl)pyridine, phenylpyrazole, 5-(2-phenylethynyl)-1,3-dihydropyrimidine-2,4-dione, 4-phenyl-1,2,3-thiadiazole, 2-(2-phenylethynyl)pyrazine, 2-phenylthiophene, phenylimidazole, 3-(2-piperazinylphenyl)furan, 3-(2,4-dichlorophenyl)-4-methylpyrrole, and the like.

Preferred optionally substituted heteroarylaryl groups include: 5-(2-phenylethynyl)pyrimidine-2-ylamine, 1-methoxy 4-(2-thienyl)benzene, 1-methoxy-3-(2-thienyl)benzene, 5-methyl-2-phenylpyridine, 5-methyl-3-phenylisoxazole, 2-[3-(trifluoromethyl)phenyl]furan, 3-fluoro-5-(2-furyl)-2-methoxy-1-prop-2-enylbenzene, (hydroxyimino)(5-phenyl(2-thienyl))methane, 5-[(4-methylpiperazinyl)methyl]-2-phenylthiophene, 2-(4-ethylphenyl)thiophene, 4-methylthio-1-(2-thienyl)benzene, 2-(3-nitrophenyl)thiophene, (tert-butoxy)-N-[(5-phenyl(3-pyridyl))methyl]carboxamide, hydroxy-N-[(5-phenyl(3-pyridyl))methyl]amide, 2-(phenylmethylthio)pyridine, and benzylimidazole.

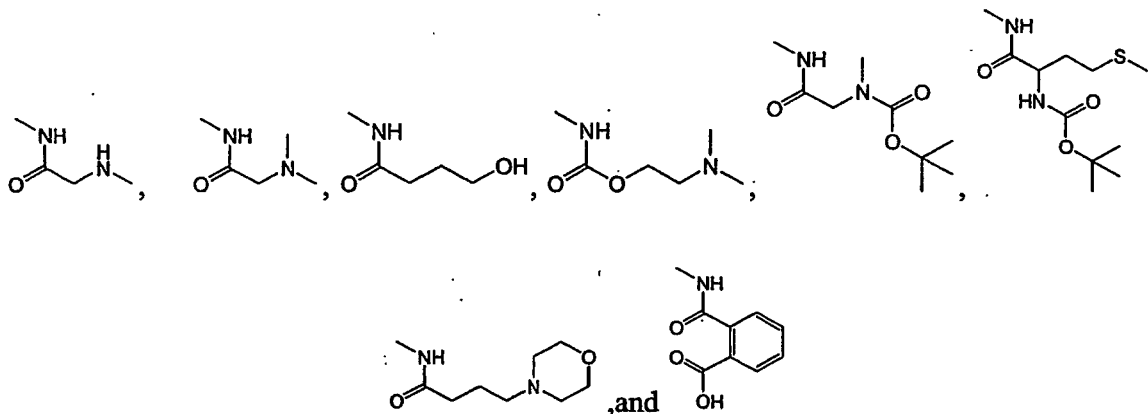
[0046] The term "heteroarylheteroaryl" refers to a biaryl group where both of the aryl groups is a heteroaryl group. Exemplary heteroarylheteroaryl groups include, for example, 3-pyridylimidazole, 2-imidazolylpyrazine. Preferred optionally substituted heteroarylheteroaryl groups include: 2-(4-piperazinyl-3-pyridyl)furan, diethyl(3-pyrazin-2-yl(4-pyridyl))amine, and dimethyl{2-[2-(5-methylpyrazin-2-yl)ethynyl](4-pyridyl)}amine.

[0047] "Optionally substituted" refers to the optional replacement of hydrogen with one or more monovalent or divalent radicals. Optionally substituted groups include those described herein, for each group in which a distinct definition for substitution is supplied. Additionally, suitable substitution groups include, for example, hydroxyl, nitro, amino, imino, cyano, halo, thio, thioamido, amidino, imidino, oxo, oxamidino, methoxamidino, imidino, guanidino, sulfonamido, carbonyl, formyl, alkyl, substituted alkyl, haloloweralkyl, loweralkoxy, haloloweralkoxy, loweralkoxyalkyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkylcarbonyl, alkylthio, aminoalkyl, cyanoalkyl, benzyl, pyridyl, pyrazolyl, pyrrole, thiophene, imidazolyl.

[0048] Representative substituted amidino and heterocycloamidino groups include, for example, those shown below. These amidino and heterocycloamidino groups can be further substituted as will be apparent to those having skill in the organic and medicinal chemistry arts in conjunction with the disclosure herein.

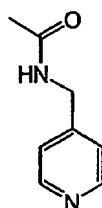


[0049] Representative substituted alkylcarbonylamino, alkyloxycarbonylamino, aminoalkyloxycarbonylamino, and arylcarbonylamino groups include, for example, those shown below. These groups can be further substituted as will be apparent to those having skill in the organic and medicinal chemistry arts in conjunction with the disclosure herein.



[0050] Representative substituted aminocarbonyl groups include, for example, those shown below. These can be further substituted by heterocyclo groups and heteroaryl groups as will be apparent to those having skill in the organic and medicinal chemistry arts in conjunction with the disclosure herein. Preferred aminocarbonyl groups include: N-(2-cyanoethyl)carboxamide, N-(3-methoxypropyl)carboxamide, N-cyclopropylcarboxamide, N-(2-hydroxy-isopropyl)carboxamide, methyl 2-carboxylamino-3-hydroxypropanoate, N-(2-hydroxypropyl)carboxamide, N-(2-hydroxyisopropyl)carboxamide, N-[2-hydroxy-1-(hydroxymethyl)ethyl]carboxamide, N-(2-carboxylaminoethyl)acetamide, N-(2-(2-pyridyl)ethyl)carboxamide, N-(2-pyridylmethyl)carboxamide, N-(oxolan-2-ylmethyl)carboxamide, N-(4-hydroxypyrrolidin-2-yl)carboxamide, N-[2-(2-hydroxyethoxy)ethyl]carboxamide, N-(4-hydroxycyclohexyl)carboxamide, N-[2-(2-oxo-4-imidazolyl)ethyl]carboxamide, N-(carbonylaminomethyl)acetamide, N-(3-pyrrolidinylpropyl)carboxamide, N-[1-(carbonylaminomethyl)pyrrolidin-3-yl]acetamide, N-(2-morpholin-4-ylethyl)carboxamide, N-[3-(2-oxopyrrolidinyl)propyl]carboxamide, 4-methyl-2-oxopiperazinecarbaldehyde, N-(2-hydroxy-3-pyrrolidinylpropyl)carboxamide, N-(2-hydroxy-3-morpholin-4-ylpropyl)carboxamide, N-{2-[(5-cyano-2-pyridyl)amino]ethyl}carboxamide, 3-(dimethylamino)pyrrolidinecarbaldehyde.





CC(=O)OC, CC(=O)OC(C)(C)C, CC(=O)OCCO, CC(=O)OCCN(C)C, CC(=O)OCCCN(C)C, CC(=O)OCCCCN(C)C,  
CC(=O)OCCN(C)CCO, CC(=O)OCCN1CCOCC1 and CC(=O)OCC(O)CN1CCOCC1

**[0053]** A "pharmaceutically acceptable salt" includes a salt with an inorganic base, organic base, inorganic acid, organic acid, or basic or acidic amino acid. As salts of inorganic bases, the invention includes, for example, alkali metals such as sodium or potassium; alkaline earth metals such as calcium and magnesium or aluminum; and ammonia. As salts of organic bases, the invention includes, for example, trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, and triethanolamine. As salts of inorganic acids, the instant invention includes, for example, hydrochloric acid, hydroboric acid, nitric acid, sulfuric acid, and phosphoric acid. As salts of organic acids, the instant invention

includes, for example, formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid. As salts of basic amino acids, the instant invention includes, for example, arginine, lysine and ornithine. Acidic amino acids include, for example, aspartic acid and glutamic acid.

**[0054]** As used herein, the term "pharmaceutically acceptable ester" refers to esters that hydrolyze in vivo and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanolic, alkenolic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Representative examples of particular esters include formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

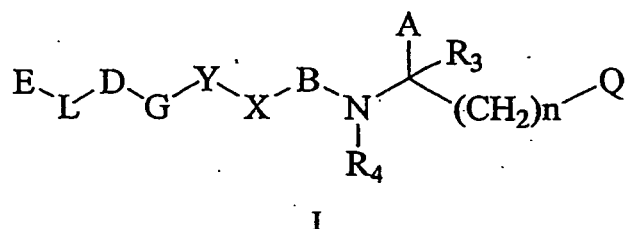
**[0055]** The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation and allergic response commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds. The term "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compound, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987.

**[0056]** The term "antibacterial agent" refers to agents synthesized or modified in the laboratory that have either bactericidal or bacteriostatic activity. An "active" agent in this context will inhibit the growth of *P. aeruginosa* and other gram-negative bacteria. The term "inhibiting the growth" indicates that the rate of increase in the numbers of a population of a particular bacterium is reduced. Thus, the term includes situations in which the bacterial population increases but at a reduced rate, as well as situations where the growth of the population is stopped, as well as situations where the numbers of the bacteria in the population are reduced or the population even eliminated. If an enzyme activity assay is used to screen for inhibitors, one can make modifications in uptake/efflux, solubility, half-life, etc. to compounds in order to correlate enzyme inhibition with growth inhibition. The activity of antibacterial agents is not necessarily limited to bacteria but may also encompass activity against parasites, virus, and fungi.

**[0057]** The subject invention also includes isotopically-labeled LpxC inhibitors, that are structurally identical to those disclosed above, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, such as  $^2\text{H}$ ,  $^3\text{H}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{O}$ ,  $^{17}\text{O}$ ,  $^{31}\text{P}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{18}\text{F}$  and  $^{36}\text{Cl}$ , respectively. Compounds of the present invention, and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as  $^3\text{H}$  and  $^{14}\text{C}$  are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e.,  $^3\text{H}$ , and carbon-14, i.e.,  $^{14}\text{C}$ , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e.,  $^2\text{H}$ , may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of this invention can generally be prepared by carrying out known or referenced procedures and by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

**[0058]** The present invention provides novel compounds, pharmaceutical formulations including the compounds compounds for use in inhibiting UDP-3-O-(R-3-hydroxydecanoyl)-N-acetylglucosamine deacetylase (LpXC), and compounds for use in treating gram-negative bacterial infections.

**[0059]** The present disclosure provides compounds of formula I:



or stereoisomers, pharmaceutically acceptable salts, esters, and prodrugs thereof, wherein E is absent or selected from the group consisting of

- (1) H,  
 (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,  
 (3) substituted or unsubstituted C<sub>2</sub>-C<sub>6</sub>-alkenyl,  
 (4) substituted or unsubstituted C<sub>2</sub>-C<sub>6</sub>-alkynyl,  
 (5) substituted or unsubstituted aryl,  
 (6) substituted or unsubstituted heterocyclyl, and  
 (7) substituted or unsubstituted heteroaryl;

L is absent or selected from the group consisting of

- (1) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,  
 (2) -(NH)<sub>0-1</sub>-(CH<sub>2</sub>)<sub>j</sub>-NR<sup>3L</sup>-(CH<sub>2</sub>)<sub>k</sub>-,  
 (3) -(NH)<sub>0-1</sub>-C(R<sup>1L</sup>, R<sup>2L</sup>)-NR<sup>3L</sup>-C(R<sup>1L</sup>, R<sup>2L</sup>)-,  
 (4) -C(R<sup>1L</sup>, R<sup>2L</sup>)-O-C(R<sup>1L</sup>, R<sup>2L</sup>)-,  
 (5) -(CH<sub>2</sub>)<sub>j</sub>-NR<sup>3L</sup>-C(R<sup>1L</sup>, R<sup>2L</sup>)-CONH-(CH<sub>2</sub>)<sub>k</sub>-,  
 (6) -CO-C(R<sup>1L</sup>, R<sup>2L</sup>)-NHCO-,  
 (7) -CONH-,  
 (8) -NHCO-,  
 wherein

R<sup>1L</sup>, R<sup>2L</sup>, and R<sup>3L</sup> are independently selected from the group consisting of

- (a) H,  
 (b) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,  
 (c) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with aryl,  
 (d) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heterocyclyl, and  
 (e) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heteroaryl,

or R<sup>1L</sup> and R<sup>3L</sup>, together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S,  
 j is an integer of 0-4;  
 k is an integer of 0-4;

D is absent or selected from the group consisting of

- (1) substituted or unsubstituted C<sub>3</sub>-C<sub>8</sub>-cycloalkyl,  
 (2) substituted or unsubstituted aryl,  
 (3) substituted or unsubstituted heterocyclyl, and  
 (4) substituted or unsubstituted heteroaryl;

G is absent or selected from the group consisting of

- (1) -(CH<sub>2</sub>)<sub>i</sub>-O-(CH<sub>2</sub>)<sub>i</sub>-,  
 (2) -(CH<sub>2</sub>)<sub>i</sub>-S-(CH<sub>2</sub>)<sub>i</sub>-,  
 (3) -(CH<sub>2</sub>)<sub>i</sub>-NR<sup>g</sup>-(CH<sub>2</sub>)<sub>i</sub>-,  
 (4) -C(=O)-,  
 (5) -NHC(=O)-,  
 (6) -C(=O)NH-,  
 (7) -(CH<sub>2</sub>)<sub>i</sub>NHCH<sub>2</sub>C(=O)NH-,  
 (8) -C≡C-,  
 (9) -C=C-C≡C-, and  
 (10) -C=C-;

wherein

R<sup>g</sup> is H or substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl;  
 i is an integer of 0-4;

Y is selected from the group consisting of

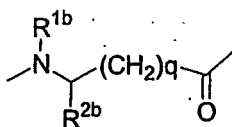
- (1) substituted or unsubstituted C<sub>3</sub>-C<sub>8</sub>-cycloalkyl,

- (2) substituted or unsubstituted aryl,
- (3) substituted or unsubstituted heterocyclyl, and
- (4) substituted or unsubstituted heteroaryl;

X is selected from the group consisting of

- (1)  $-(C=O)-$ ,
- (2)  $-C_1-C_6\text{-alkyl}-(C=O)-$ ,
- (3)  $-C_2-C_6\text{-alkenyl}-(C=O)-$ ,
- (4)  $-C_2-C_6\text{-alkynyl}-(C=O)-$ , and
- (5)  $-CH_2-$ ;

or when B is absent, X and A, together with the atoms to which they are attached can form a heterocyclic ring, having from 5 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S; B is a absent or



wherein  $R^{1b}$  and  $R^{2b}$ , are independently selected from the group consisting of

- (a) H,
- (b) substituted or unsubstituted  $C_1-C_6\text{-alkyl}$ ,
- (c) substituted or unsubstituted  $C_2-C_6\text{-alkenyl}$ ,
- (d) substituted or unsubstituted  $C_2-C_6\text{-alkynyl}$ ,
- (e) substituted or unsubstituted aryl,
- (f) substituted or unsubstituted heterocyclyl,
- (g) substituted or unsubstituted heteroaryl,
- (h)  $C_1-C_6\text{-alkyl}$  substituted with aryl,
- (i)  $C_1-C_6\text{-alkyl}$  substituted with heterocyclyl, and
- (j)  $C_1-C_6\text{-alkyl}$  substituted with heteroaryl,

or  $R^{1b}$  and  $R^{2b}$ , together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S; q is an integer of 0-4;

$R_3$  is H or substituted or unsubstituted  $C_1-C_6\text{-alkyl}$ ,

or  $R_3$  and A, together with the atoms to which they are attached can form a substituted or unsubstituted 3-10 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S;

$R_4$  is H or substituted or unsubstituted  $C_1-C_6\text{-alkyl}$ ,

or  $R_4$  and A, together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S;

n is an integer of 0-2;

A is selected from the group consisting of

- (1) H,
- (2)  $-(CH_2)_rC(R^{1a}, R^{2a})(CH_2)_sOR^{3a}$ ,
- (3)  $-(CH_2)_rC(R^{1a}, R^{2a})N(R^{4a}, R^{5a})$ ,
- (4)  $-(CH_2)_rC(R^{1a}, R^{2a})N(R^{4a})COR^{3a}$ ,
- (5)  $-(CH_2)_rC(R^{1a}, R^{2a})NHCON(R^{4a}, R^{5a})$ ,
- (6)  $-(CH_2)_rC(R^{1a}, R^{2a})NHC(=NH)N(R^{4a}, R^{5a})$ ,
- (7)  $-CH(R^{1a}, R^{2a})$ ,
- (8)  $-C\equiv CH$ ,
- (9)  $-(CH_2)_rC(R^{1a}, R^{2a})CN$ ,
- (10)  $-(CH_2)_rC(R^{1a}, R^{2a})CO_2R^{3a}$ , and
- (11)  $-(CH_2)_rC(R^{1a}, R^{2a})CN(R^{4a}, R^{5a})$ ,

wherein R<sup>1a</sup>, R<sup>2a</sup>, R<sup>3a</sup>, R<sup>4a</sup>, and R<sup>5a</sup> are independently selected from the group consisting of

- (a) H,
- (b) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
- (c) substituted or unsubstituted aryl,
- (d) substituted or unsubstituted heterocyclyl,
- (e) substituted or unsubstituted heteroaryl,
- (f) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with aryl,
- (g) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heterocyclyl, and
- (h) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heteroaryl,

or R<sup>4a</sup> and R<sup>5a</sup> together with the N atom to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S;

r is an integer of 0-4;

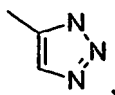
s is an integer of 0-4;

Q is absent or selected from the group consisting of

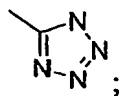
- (1) -C(=O)N(R<sub>1</sub>, R<sub>2</sub>),
- (2) -NHC(=O)N(R<sub>1</sub>, R<sub>2</sub>),
- (3) -N(OH)C(=O)N(R<sub>1</sub>, R<sub>2</sub>),
- (4) -CH(OH)C(=O)N(R<sub>1</sub>, R<sub>2</sub>),
- (5) -CH[N(R<sup>2q</sup>, R<sup>3q</sup>)]C(=O)N(R<sub>1</sub>, R<sub>2</sub>),
- (6) -CHR<sup>1q</sup>C(=O)N(R<sub>1</sub>, R<sub>2</sub>),
- (7) -CO<sub>2</sub>H,
- (8) -C(=O)NHSO<sub>2</sub>R<sup>4q</sup>,
- (9) -SO<sub>2</sub>NH<sub>2</sub>,
- (10) -N(OH)C(=O)R<sup>1q</sup>,
- (11) -N(OH)SO<sub>2</sub>R<sup>4q</sup>,
- (12) -NHSO<sub>2</sub>R<sup>4q</sup>,
- (13) -SH,
- (14) -CH(SH)(CH<sub>2</sub>)<sub>0-1</sub>C(=O)N(R<sub>1</sub>, R<sub>2</sub>),
- (15) -CH(SH)(CH<sub>2</sub>)<sub>0-1</sub>CO<sub>2</sub>H,
- (16) -CH(OH)(CH<sub>2</sub>)<sub>0-1</sub>CO<sub>2</sub>H,
- (17) -CH(SH)CH<sub>2</sub>CO<sub>2</sub>R<sup>1q</sup>,
- (18) -CH(OH)(CH<sub>2</sub>)-SO<sub>2</sub>NH<sub>2</sub>,
- (19) -CH(CH<sub>2</sub>SH)NHCOR<sup>1q</sup>,
- (20) -CH(CH<sub>2</sub>SH)NHSO<sub>2</sub>R<sup>4q</sup>,
- (21) -CH(CH<sub>2</sub>SR<sup>5q</sup>)CO<sub>2</sub>H,
- (22) -CH(CH<sub>2</sub>SH)NHSO<sub>2</sub>NH<sub>2</sub>,
- (23) -CH(CH<sub>2</sub>OH)CO<sub>2</sub>H,
- (24) -CH(CH<sub>2</sub>OH)NHSO<sub>2</sub>NH<sub>2</sub>,
- (25) -C(=O)CH<sub>2</sub>CO<sub>2</sub>H,
- (26) -C(=O)(CH<sub>2</sub>)<sub>0-1</sub>CONH<sub>2</sub>,
- (27) -OSO<sub>2</sub>NHR<sup>5q</sup>,
- (28) -SO<sub>2</sub>NHNH<sub>2</sub>,
- (29) -P(=O)(OH)<sub>2</sub>,
- (30)



(31)



and  
(32)



$R_1$  is selected from the group consisting of

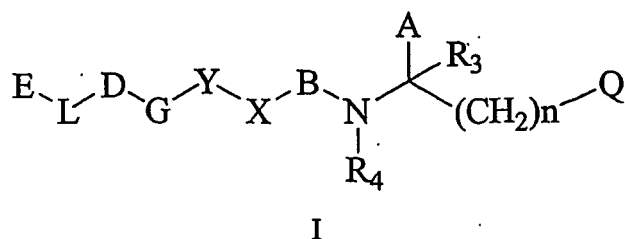
- (1) -H,
- (2) -OH,
- (3) -OC<sub>1-6</sub>-alkyl,
- (4) -N(R<sup>2q</sup>, R<sup>3q</sup>), and
- (5) substituted or unsubstituted C<sub>1-6</sub>-alkyl;

$R_2$  is selected from the group consisting of

- (1) H,
- (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
- (3) substituted or unsubstituted C<sub>2</sub>-C<sub>6</sub>-alkenyl,
- (4) substituted or unsubstituted C<sub>2</sub>-C<sub>6</sub>-alkenyl,
- (5) substituted or unsubstituted aryl,
- (6) substituted or unsubstituted heterocyclyl,
- (7) substituted or unsubstituted heteroaryl,
- (8) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with aryl,
- (9) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heterocyclyl, and
- (10) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heteroaryl,

or  $R^1$  and  $R^2$ , together with the N atom to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 10 ring atoms, wherein 1-4 ring atoms of the heterocyclic ring system are selected from N, O and S,  $R^{1q}$ ,  $R^{2q}$ ,  $R^{3q}$ ,  $R^{4q}$ , and  $R^{5q}$  are selected from H or C<sub>1</sub>-C<sub>6</sub> alkyl, wherein B is absent, or E, L, G, and B are absent, or E, L, and G are absent, or E, L, and B are absent, or E, L, D, G, and B are absent.

**[0060]** In another aspect, the present disclosure provides compounds of formula I:



or stereoisomers, pharmaceutically acceptable salts, esters, and prodrugs thereof, wherein E is absent or selected from the group consisting of

- (1) H,
  - (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
  - (3) substituted or unsubstituted aryl,
  - (4) substituted or unsubstituted heterocyclyl, and
  - (5) substituted or unsubstituted heteroaryl;
- L is absent or selected from the group consisting of
- (1) -(CH<sub>2</sub>)<sub>j</sub>-NR<sup>3L</sup>-(CH<sub>2</sub>)<sub>k</sub>-,
  - (2) -C(R<sup>1L</sup>, R<sup>2L</sup>)<sub>j</sub>-NR<sup>3L</sup>-C(R<sup>1L</sup>, R<sup>2L</sup>)<sub>k</sub>-,
  - (3) -C(R<sup>1L</sup>, R<sup>2L</sup>)<sub>j</sub>-O-C(R<sup>1L</sup>, R<sup>2L</sup>)<sub>k</sub>-,
  - (4) -(CH<sub>2</sub>)<sub>j</sub>-NR<sup>3L</sup>-C(R<sup>1L</sup>, R<sup>2L</sup>)<sub>k</sub>-CONH-(CH<sub>2</sub>)<sub>k</sub>-,

(5) -CO-(R<sup>1L</sup>, R<sup>2L</sup>)-NHCO-,

(6) -CONH-, and

(7) -NHCO-,

wherein

R<sup>1L</sup>, R<sup>2L</sup>, R<sup>3L</sup> are independently selected from the group consisting of

(a) H,

(b) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,

(c) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with aryl,

(d) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heterocyclyl,

(e) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heteroaryl,

or R<sup>1L</sup> and R<sup>3L</sup>, together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 5 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S;

j is an integer of 0-4;

k is an integer of 0-4;

D is absent or selected from the group consisting of

(1) substituted or unsubstituted C<sub>3</sub>-C<sub>8</sub>-cycloalkyl,

(2) substituted or unsubstituted aryl,

(3) substituted or unsubstituted heterocyclyl,

(4) substituted or unsubstituted heteroaryl, and G is absent or selected from the group consisting of

(1) -C(=O)-,

(2) -NHC(=O)-,

(3) -C(=O)NH-,

(4) -(CH<sub>2</sub>)<sub>i</sub>NHCH<sub>2</sub>C(=O)NH-,

(5) -C=C-, and

(6) -C≡C-C≡C-,

wherein i is an integer of 0-4;

Y is selected from the group consisting of

(1) substituted or unsubstituted C<sub>3</sub>-C<sub>8</sub>-cycloalkyl,

(2) substituted or unsubstituted aryl,

(3) substituted or unsubstituted heterocyclyl, and

(4) substituted or unsubstituted heteroaryl;

X is selected from the group consisting of

(1) -(C=O)-,

(2) -C<sub>1</sub>-C<sub>6</sub>-alkyl-(C=O)-,

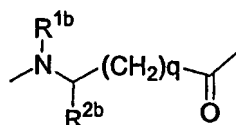
(3) -C<sub>2</sub>-C<sub>6</sub>-alkenyl-(C=O)-,

(4) -C<sub>2</sub>-C<sub>6</sub>-alkynyl-(C=O)-, and

(5) -CH<sub>2</sub>-;

or when B is absent, X and A, together with the atoms to which they are attached can form a heterocyclic ring, having from 5 to 8 ring atoms, wherein 1-2, ring atoms of the heterocyclic ring system are selected from N, O and S;

B is absent or



wherein R<sup>1b</sup> and R<sup>2b</sup> are independently selected from the group consisting of

- (a) H  
 (b) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,  
 (c) substituted or unsubstituted C<sub>2</sub>-C<sub>6</sub>-alkenyl,  
 (d) substituted or unsubstituted C<sub>2</sub>-C<sub>6</sub>-alkenyl,  
 (e) substituted or unsubstituted aryl,  
 (f) substituted or unsubstituted heterocyclyl,  
 (g) substituted or unsubstituted heteroaryl,  
 (h) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with aryl,  
 (i) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heterocyclyl, and  
 (j) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heteroaryl,  
 or R<sup>1b</sup> and R<sup>2b</sup>, together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 5 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S;

q is an integer of 0-2;

- R<sub>3</sub> is H or substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,  
 or R<sub>3</sub> and A, together with the atoms to which they are attached can form a substituted or unsubstituted 3-10 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S;  
 R<sub>4</sub> is H or substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,  
 or R<sub>4</sub> and A, together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 5 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S; .  
 A is selected from the group consisting of

- (1) H,  
 (2) -(CH<sub>2</sub>)<sub>r</sub>C(R<sup>1a</sup>, R<sup>2a</sup>)(CH<sub>2</sub>)<sub>s</sub>OR<sup>3a</sup>,  
 (3) -(CH<sub>2</sub>)<sub>r</sub>C(R<sup>1a</sup>, R<sup>2a</sup>)N(R<sup>4a</sup>, R<sup>5a</sup>),  
 -(CH<sub>2</sub>)<sub>r</sub>C(R<sup>1a</sup>, R<sup>2a</sup>)N(R<sup>4a</sup>)COR<sup>3a</sup>,  
 (5) -(CH<sub>2</sub>)<sub>r</sub>C(R<sup>1a</sup>, R<sup>2a</sup>)NHCON(R<sup>4a</sup>, R<sup>5a</sup>),  
 (6) -(CH<sub>2</sub>)<sub>r</sub>C(R<sup>1a</sup>, R<sup>2a</sup>)NHC(=NH)N(R<sup>4a</sup>, R<sup>5a</sup>),  
 (7) -CH(R<sup>1a</sup>, R<sup>2a</sup>),  
 (8) -C≡CH,  
 (9) -(CH<sub>2</sub>)<sub>r</sub>C(R<sup>1a</sup>, R<sup>2a</sup>)CN, and  
 (10) -(CH<sub>2</sub>)<sub>r</sub>C(R<sup>1a</sup>, R<sup>2a</sup>)COZR<sup>3a</sup>,

wherein R<sup>1a</sup>, R<sup>2a</sup>, R<sup>3a</sup>, R<sup>4a</sup>, and R<sup>5a</sup>, are independently selected from the group consisting of

- (a) H,  
 (b) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,  
 (c) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with aryl,  
 (d) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heterocyclyl, and  
 (e) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heteroaryl,  
 or R<sup>4a</sup> and R<sup>5a</sup>, together with the N atom to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 5 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S;

r is an integer of 0-4;

Q is absent or selected from the group consisting of

- (1) -C(=O)N(R<sub>1</sub> R<sub>2</sub>),  
 (2) -NHC(=O)N(R<sub>1</sub>, R<sub>2</sub>),  
 (3) -N(OH)C(=O)N(R<sub>1</sub>, R<sub>2</sub>),  
 (4) -CH(OH)C(=O)N(R<sub>1</sub>, R<sub>2</sub>),  
 (5) -CH[N(R<sup>2q</sup>, R<sup>3q</sup>)]C(=O)N(R<sub>1</sub>, R<sub>2</sub>), and  
 (6) -CHR<sup>1q</sup>C(=O)N(R<sub>1</sub>, R<sub>2</sub>),

R<sub>1</sub> is selected from the group consisting of

- (1) H,

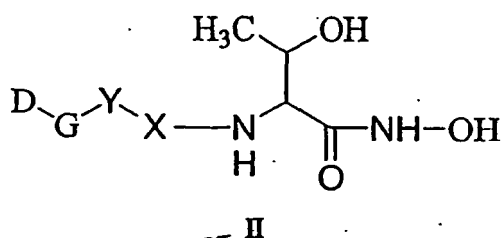


- (2) OH,  
 (3) OC<sub>1-6</sub>-alkyl,  
 (4) N(R<sup>2q</sup>, R<sup>3q</sup>), and  
 (5) substituted or unsubstituted C<sub>1-6</sub>-alkyl;

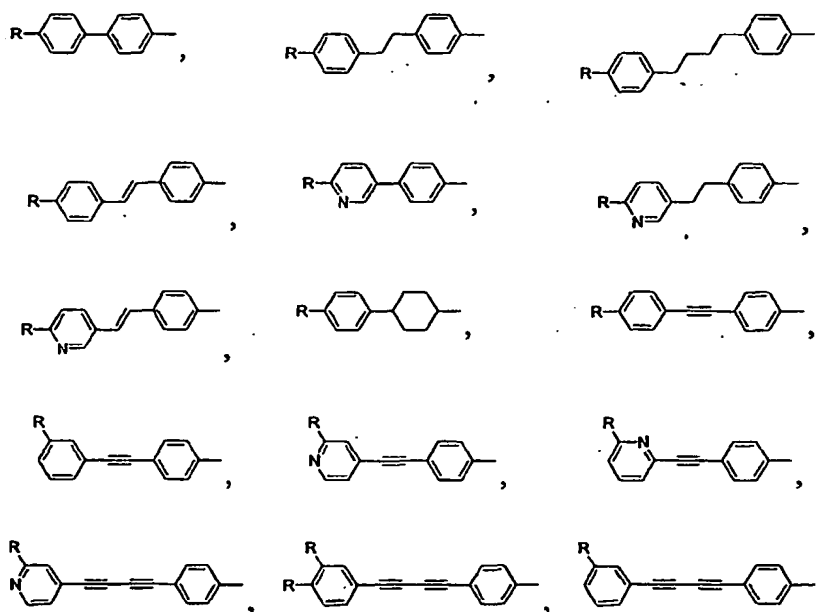
R<sub>2</sub> is selected from the group consisting of

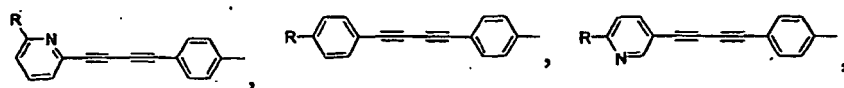
- (1) H,  
 (2) substituted or unsubstituted C<sub>1-6</sub>-alkyl,  
 (3) substituted or unsubstituted aryl,  
 (4) substituted or unsubstituted heterocyclyl,  
 (5) substituted or unsubstituted heteroaryl,  
 (6) C<sub>1-6</sub>-alkyl substituted with aryl,  
 (7) C<sub>1-6</sub>-alkyl substituted with heterocyclyl, and  
 (8) C<sub>1-6</sub>-alkyl substituted with heteroaryl,  
 or R<sup>1</sup> and R<sup>2</sup>, together with the N atom to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 10 ring atoms, wherein 1-4 ring atoms of the heterocyclic ring system are selected from N, O and S,  
 R<sup>1q</sup>, R<sup>2q</sup>, and R<sup>3q</sup> are selected from H or C<sub>1-6</sub> alkyl,  
 wherein B is absent, or E, L, G, and B are absent, or E, L, and G are absent, or E, L, and B are absent, or E, L, D, G, and B are absent.

**[0061]** In an embodiment, the present invention provides compounds of formula II:

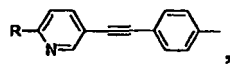


or a stereoisomer, pharmaceutically acceptable salt or ester thereof, wherein D-G-Y taken together, is selected from the group consisting of

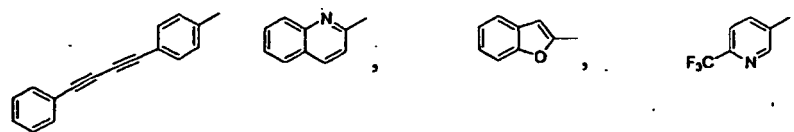
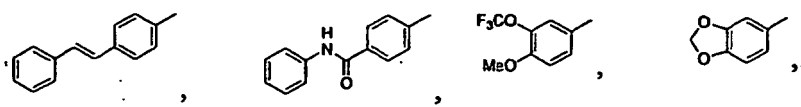
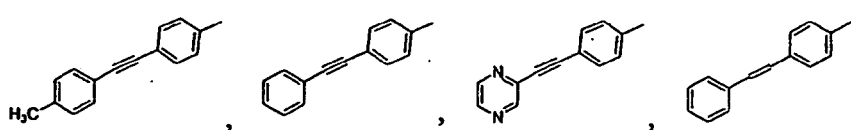
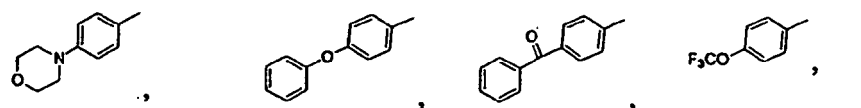
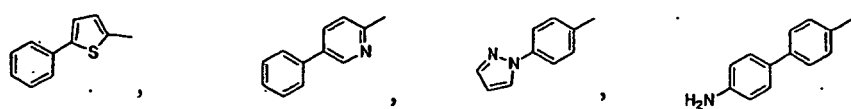
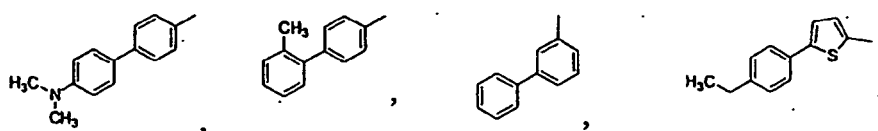
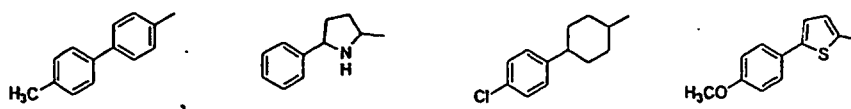
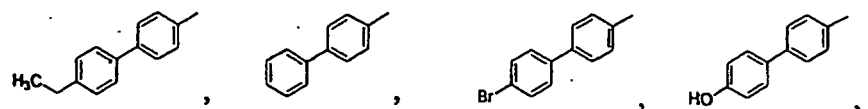


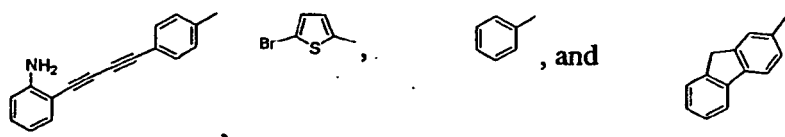


and



or





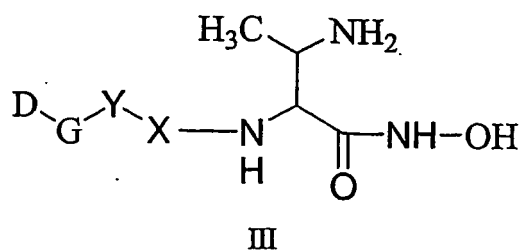
Wherein

R is selected from the group consisting of -CH<sub>3</sub>, -C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>OH, -OH, -CH<sub>3</sub>, -OC<sub>2</sub>H<sub>5</sub>, -OCF<sub>3</sub>, -CN, NO<sub>2</sub>, -CO<sub>2</sub>H, -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, NH<sub>2</sub>, -F, -Cl, -Br, -CF<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -NHSO<sub>2</sub>CH<sub>3</sub>, and NHCOCH<sub>3</sub>;

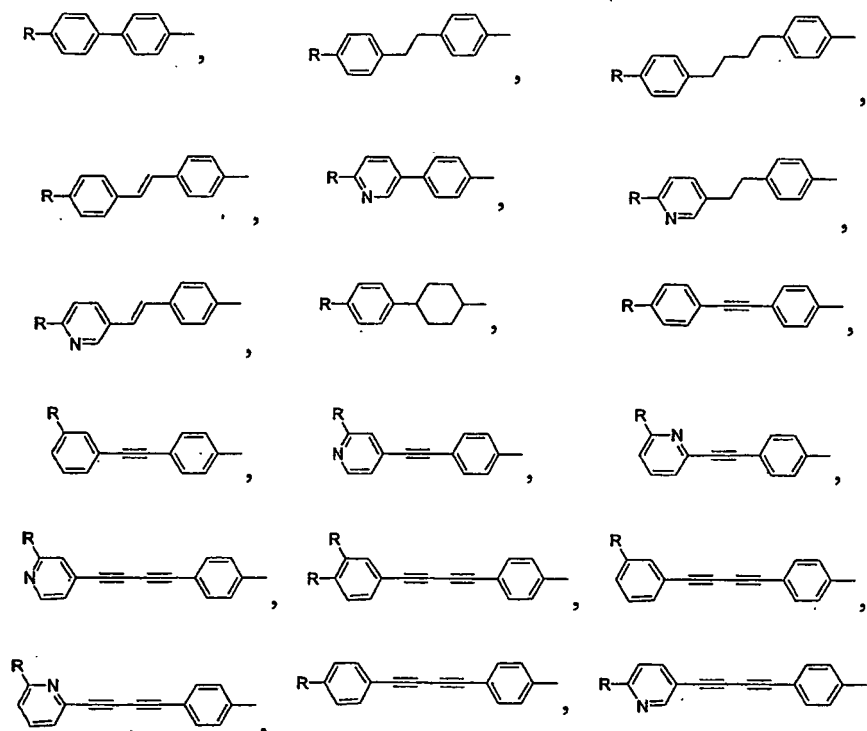
X is selected from the group consisting of

- (1) -(C=O)-,
- (2) -C<sub>1</sub>-C<sub>6</sub>-alkyl-(C=O)-, and
- (3) -C<sub>2</sub>-C<sub>6</sub>-alkenyl-(C=O)-

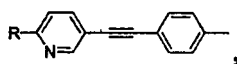
**[0062]** In another aspect, the present disclosure provides compounds of formula III:



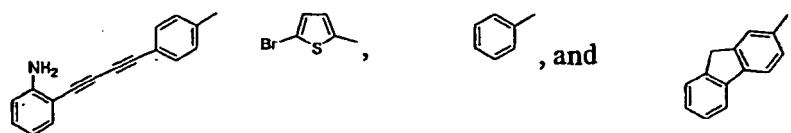
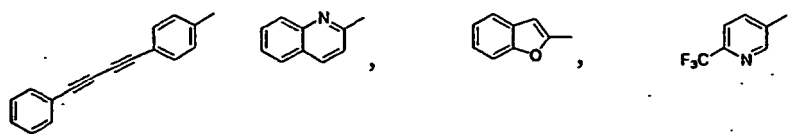
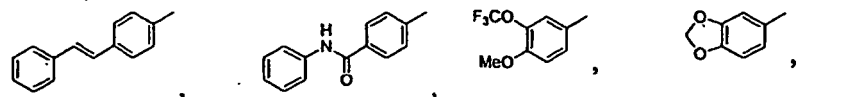
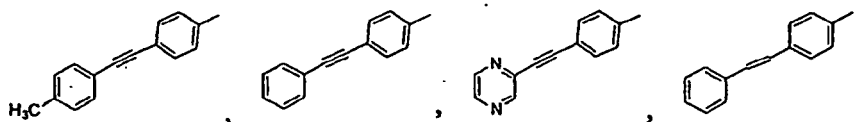
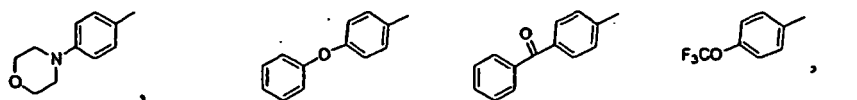
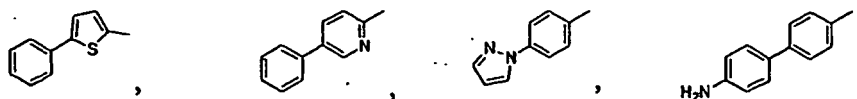
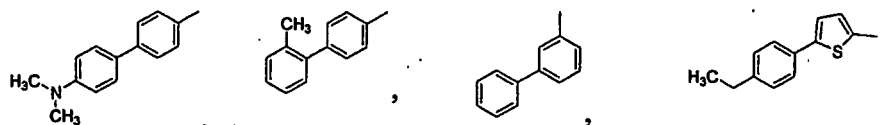
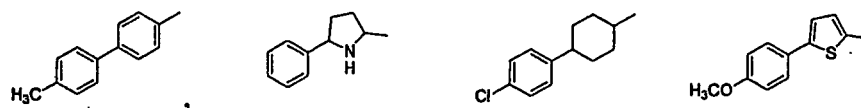
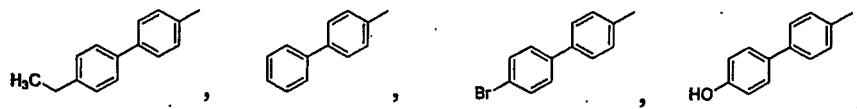
or stereoisomers, pharmaceutically acceptable salts, esters, and prodrugs thereof, wherein D-G-Y taken together, is selected from the group consisting of



and



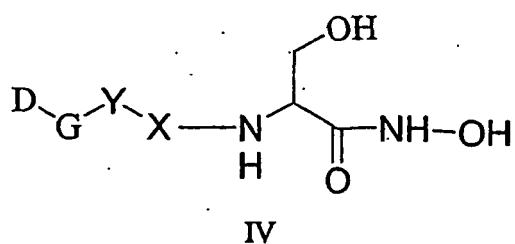
or



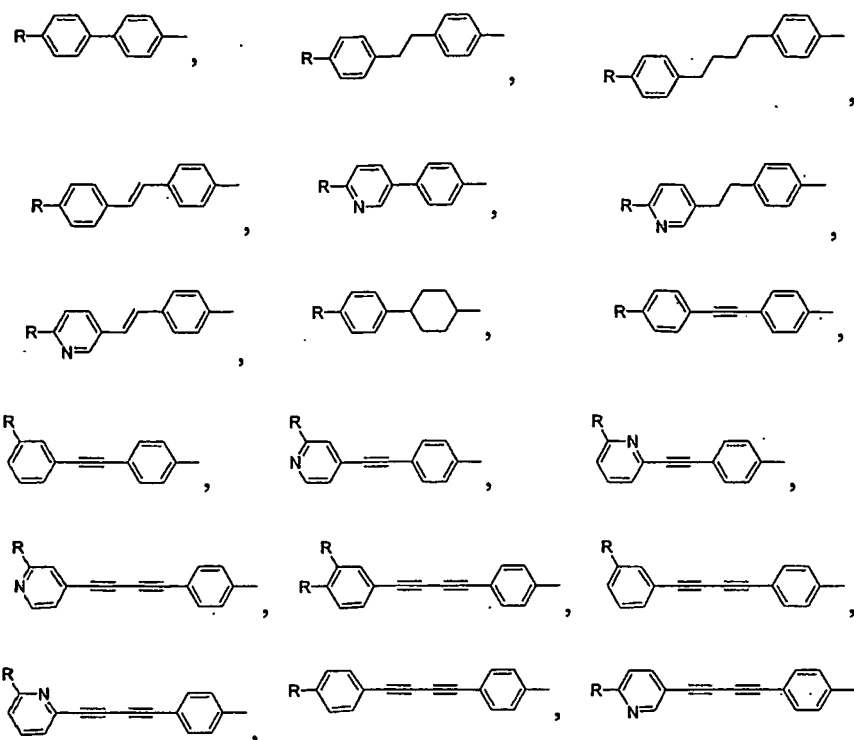
Wherein R is selected from the group consisting of -CH<sub>3</sub>, -C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>OH, -OH, -OCH<sub>3</sub>, -OC<sub>2</sub>H<sub>5</sub>, -OCF<sub>3</sub>, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>H, -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, -NH<sub>2</sub>, F, -Cl, -Br, -CF<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, NHSO<sub>2</sub>CH<sub>3</sub>, and -NHCOCH<sub>3</sub>; X is selected from the groups consisting of

- (1) -(C=O)-,
- (2) -C<sub>1</sub>-C<sub>6</sub>-alkyl-(C=O)-, and
- (3) -C<sub>2</sub>-C<sub>6</sub>-alkenyl-(C=O)-

[0063] In another aspect, the present disclosure provides compounds of formula IV:



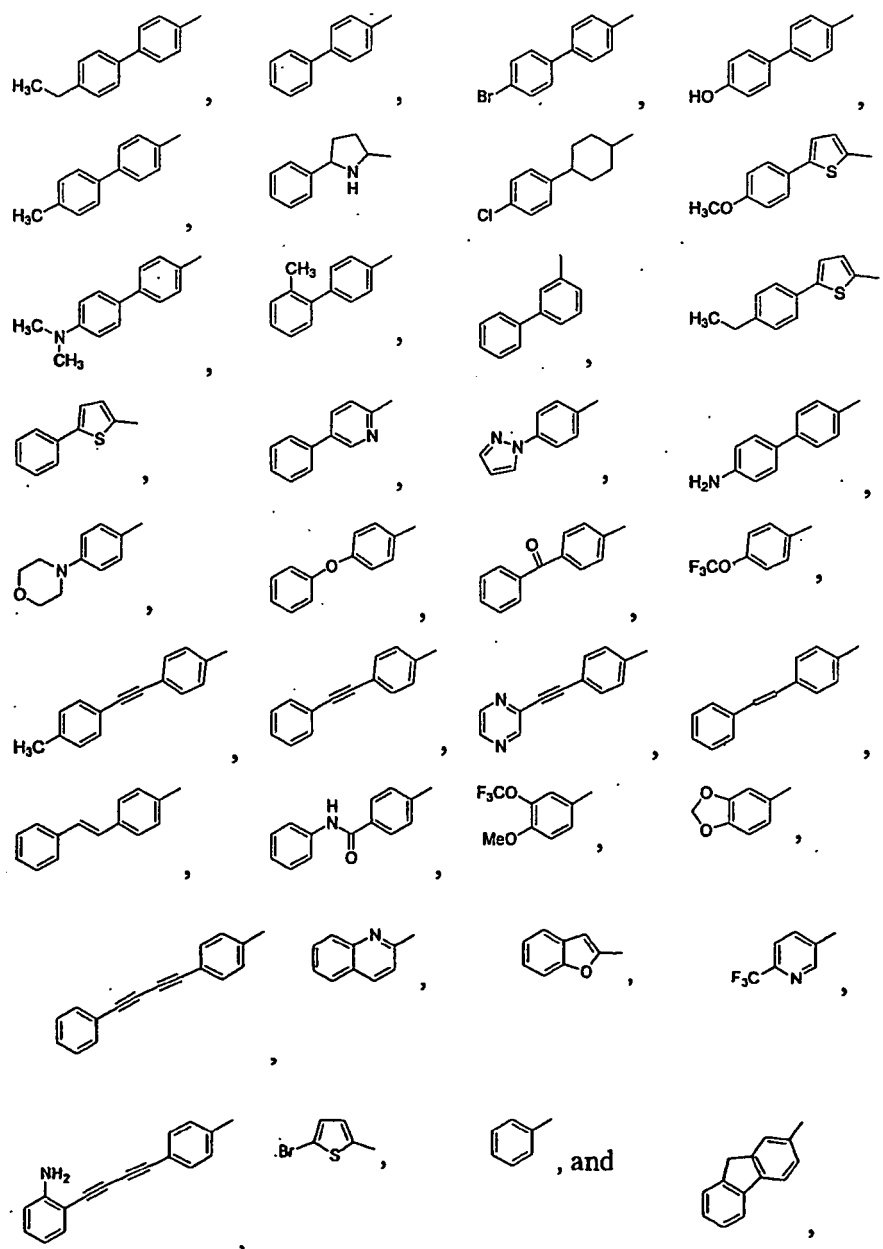
or stereoisomers, pharmaceutically acceptable salts, esters, and prodrugs thereof, wherein D-G-Y taken together, is selected from the group consisting of



and



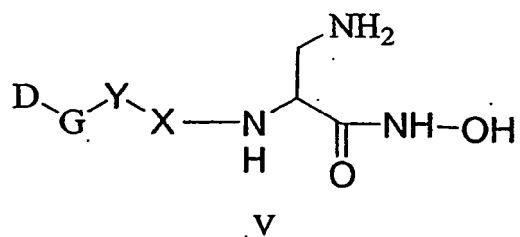
or



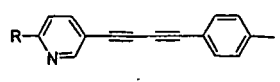
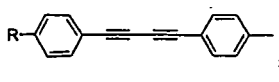
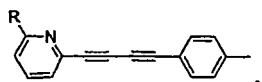
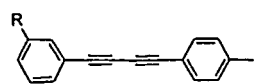
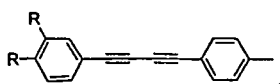
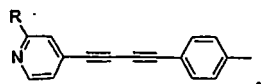
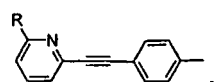
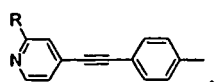
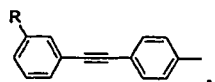
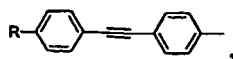
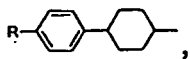
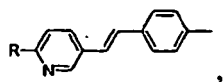
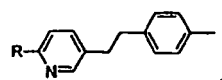
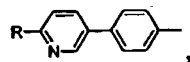
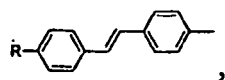
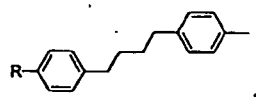
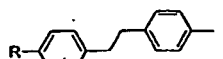
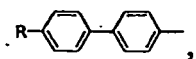
Wherein R is selected from the group consisting of -CH<sub>3</sub>, -C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>OH, -OH, -OCH<sub>3</sub>, -OC<sub>2</sub>H<sub>5</sub>, -OCF<sub>3</sub>, -CN, NO<sub>2</sub>, -CO<sub>2</sub>H, -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, -NH<sub>2</sub>, F, -Cl, -Br, -CF<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -NHSO<sub>2</sub>CH<sub>3</sub> and -NHCOCH<sub>3</sub>; X is selected from the groups consisting of

- (1) -(C=O)-,
- (2) -C<sub>1</sub>-C<sub>6</sub>-alkyl-(C=O)-, and
- (3) -C<sub>2</sub>-C<sub>6</sub>-alkenyl-(C=O)-

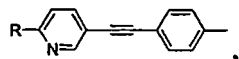
**[0064]** In another aspect, the present disclosure provides compounds of formula V:



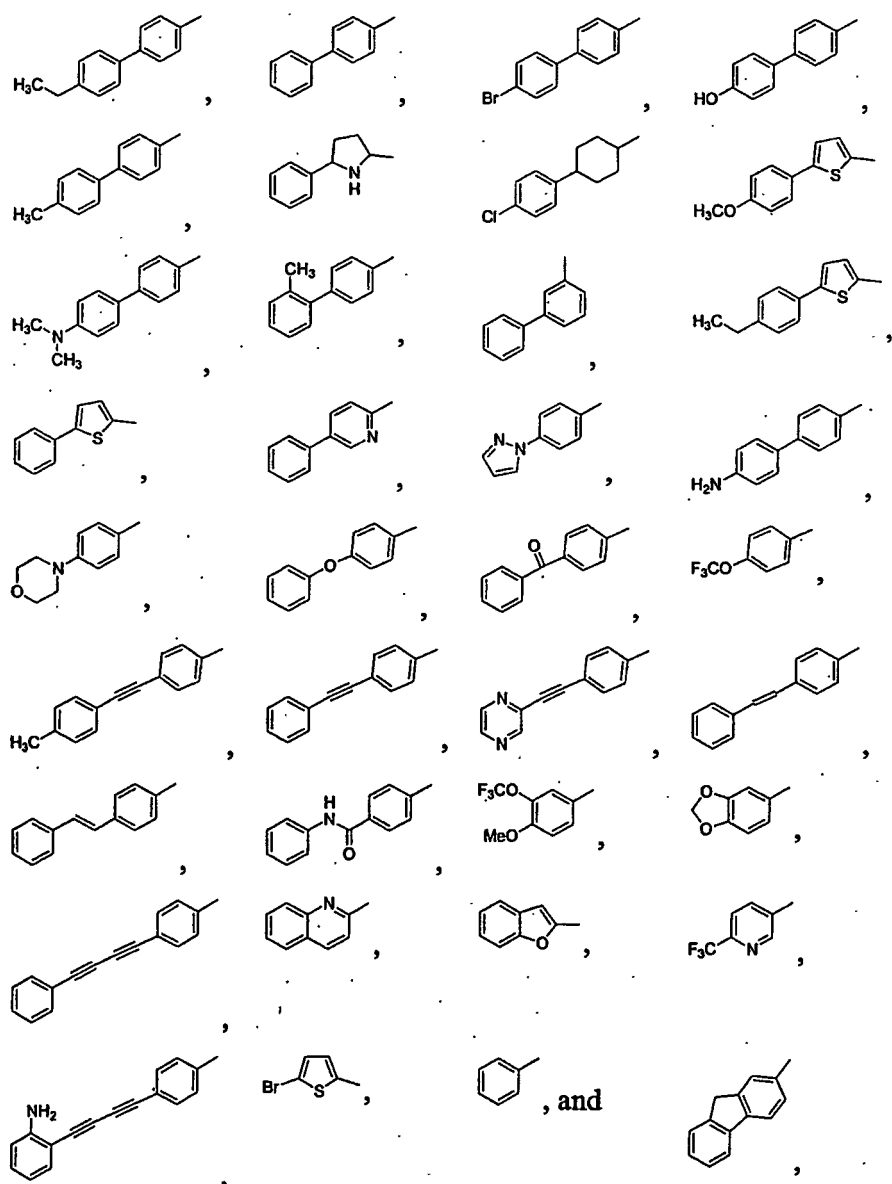
or stereoisomers, pharmaceutically acceptable salts, esters, and prodrugs thereof, wherein D-G-Y taken together, is selected from the group consisting of



and



or



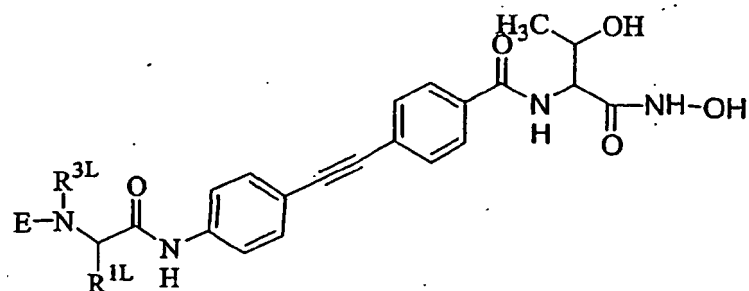
Wherein

R is selected from the group consisting of -CH<sub>3</sub>, -C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>OH, -OH, -OCH<sub>3</sub>, -OC<sub>2</sub>H<sub>5</sub>, -OCF<sub>3</sub>, -CN, NO<sub>2</sub>, -CO<sub>2</sub>H, -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, -NH<sub>2</sub>, -F, -Cl, -Br, -CF<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -NHSO<sub>2</sub>CH<sub>3</sub>, and NHCOCH<sub>3</sub>;

X is selected from the groups consisting of

- (1) -(C=O)-,
- (2) -C<sub>1</sub>-C<sub>6</sub>-alkyl-(C=O)-, and
- (3) -C<sub>2</sub>-C<sub>6</sub>-alkenyl-(C=O)-In another embodiment, the present invention provides compounds of formula VI:





VI

or a stereoisomer pharmaceutically acceptable salt, or ester thereof, wherein E is absent or selected from the group consisting of

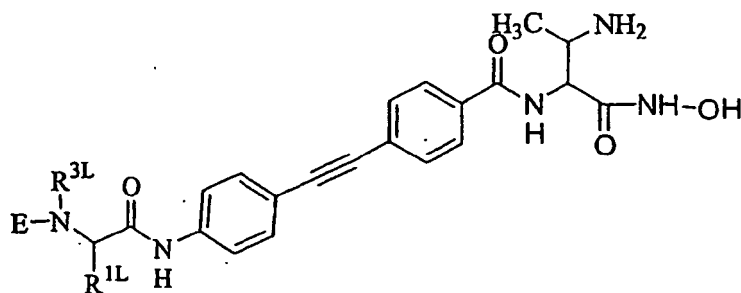
- (1) H,
  - (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
  - (3) substituted or unsubstituted aryl,
  - (4) substituted or unsubstituted heterocyclyl, and
  - (5) substituted or unsubstituted heteroaryl,
- or E and R<sup>3L</sup> together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 10 ring atoms, wherein 1-4 ring atoms of the heterocyclic ring system are selected from N, O and S,

R<sup>1L</sup>, R<sup>3L</sup> are independently selected from the group consisting of

- (1) H,
- (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
- (3) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with aryl,
- (4) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heterocyclyl, and
- (5) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heteroaryl,

or R<sup>1L</sup> and R<sup>3L</sup>, together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S.

**[0065]** In another aspect, the present disclosure provides compounds of formula VII:



VII

or stereoisomers, pharmaceutically acceptable salts, esters, and prodrugs thereof, wherein E is absent or selected from the group consisting of

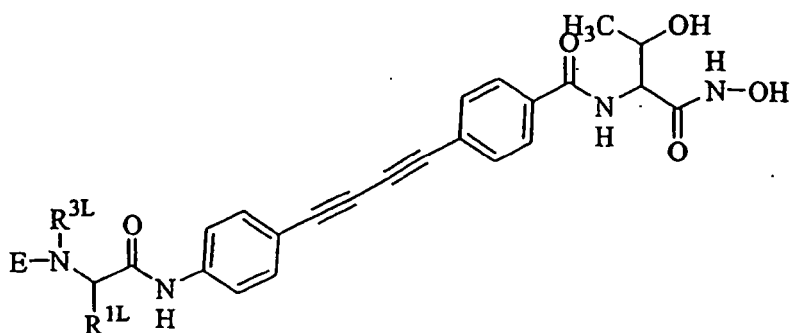
- (1) H,
  - (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
  - (3) substituted or unsubstituted aryl,
  - (4) substituted or unsubstituted heterocyclyl, and
  - (5) substituted or unsubstituted heteroaryl,
- or E and R<sup>3L</sup>, together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic

ring, having from 3 to 10 ring atoms, wherein 1-4 ring atoms of the heterocyclic ring system are selected from N, O and S;

R<sup>1L</sup>, R<sup>3L</sup> are independently selected from the group consisting of

- (1) H,
- (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
- (3) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with aryl,
- (4) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heterocyclyl, and
- (5) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heteroaryl,

or R<sup>1L</sup>, and R<sup>3L</sup>, together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S.  
**[0066]** In another embodiment, the present invention provides compounds of formula VIII:



VIII

or a stereoisomer, pharmaceutically acceptable salt, or ester thereof, wherein E is absent or selected from the group consisting of

- (1) H,
- (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
- (3) substituted or unsubstituted aryl,
- (4) substituted or unsubstituted heterocyclyl, and
- (5) substituted or unsubstituted heteroaryl,

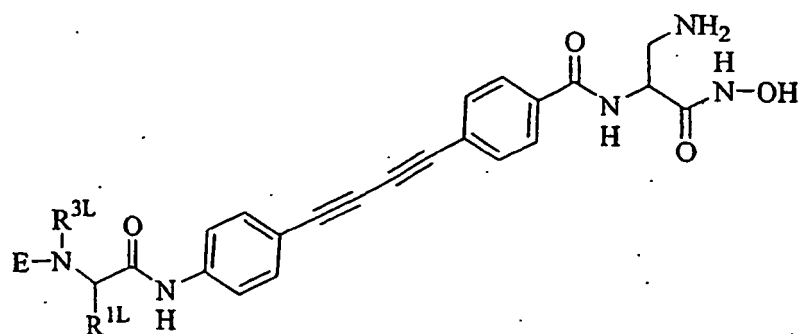
or E and R<sup>3L</sup>, together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 10 ring atoms, wherein 1-4 ring atoms of the heterocyclic ring system are selected from N, O and S;

R<sup>1L</sup>, R<sup>3L</sup> are independently selected from the group consisting of

- (1) H,
- (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
- (3) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with aryl,
- (4) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heterocyclyl, and
- (5) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heteroaryl,

or R<sup>1L</sup> and R<sup>3L</sup> together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S.

**[0067]** In another aspect, the present disclosure provides compounds of formula IX:



IX

or stereoisomers, pharmaceutically acceptable salts, esters, and prodrugs thereof, wherein E is absent or selected from the group consisting of

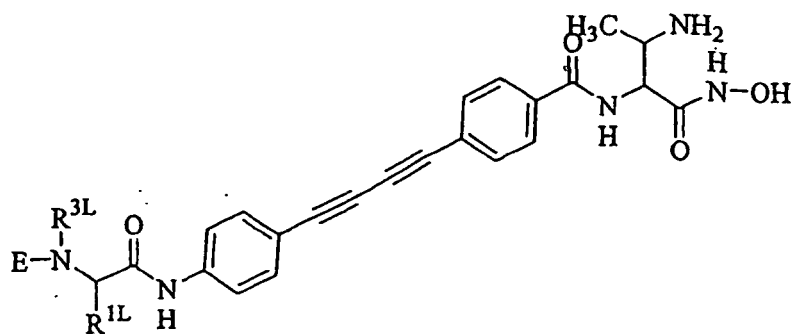
- (1) H,
  - (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
  - (3) substituted or unsubstituted aryl,
  - (4) substituted or unsubstituted heterocyclyl, and
  - (5) substituted or unsubstituted heteroaryl,
- or E and R<sup>3L</sup> together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 10 ring atoms, wherein 1-4 ring atoms of the heterocyclic ring system are selected from N, O and S;

R<sup>1L</sup>, R<sup>3L</sup> are independently selected from the group consisting of

- (1) H,
- (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
- (3) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with aryl,
- (4) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heterocyclyl, and
- (5) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heteroaryl,

or R<sup>1L</sup> and R<sup>3L</sup>, together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S.

**[0068]** In another aspect, the present disclosure provides compounds of formula X:



X

or stereoisomers, pharmaceutically acceptable salts, esters, and prodrugs thereof, wherein E is absent or selected from the group consisting of

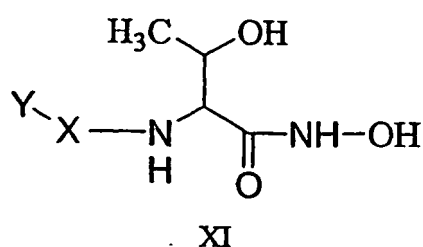
- (1) H,
- (2) substituted or unsubstituted C<sub>1</sub>C<sub>6</sub>-alkyl,
- (3) substituted or unsubstituted aryl,

(4) substituted or unsubstituted heterocyclyl, and  
 (5) substituted or unsubstituted heteroaryl,  
 or E and R<sup>3L</sup>, together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic  
 ring, having from 3 to 10 ring atoms, wherein 1-4 ring atoms of the heterocyclic ring system are selected from N, O  
 and S;

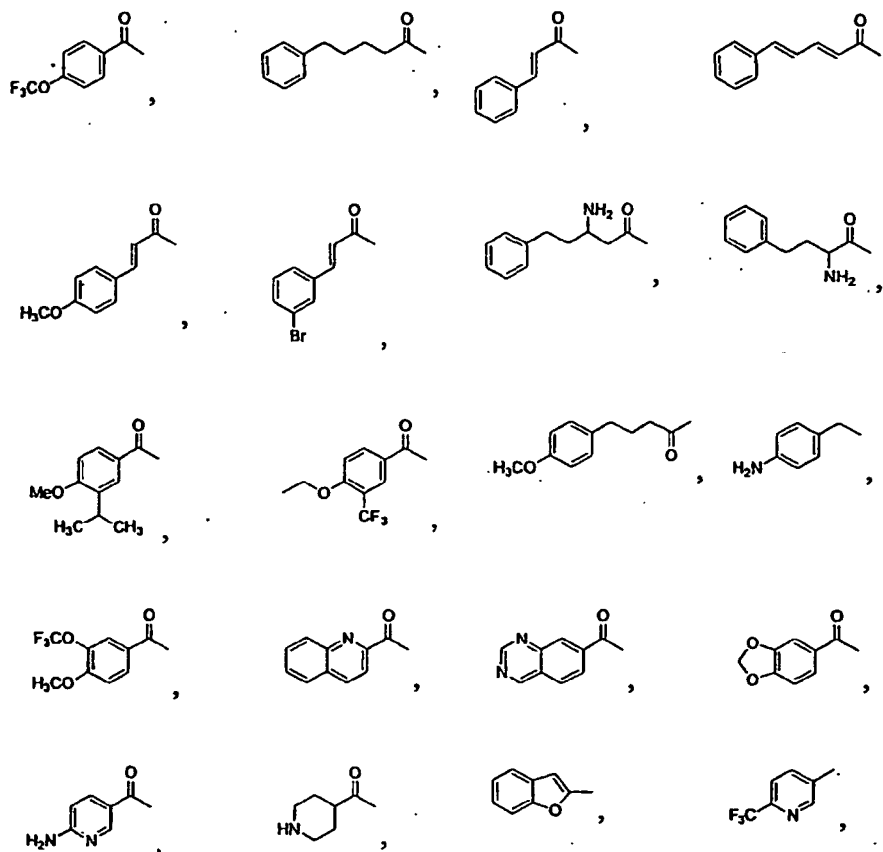
R<sup>1L</sup>, R<sup>3L</sup> are independently selected from the group consisting of

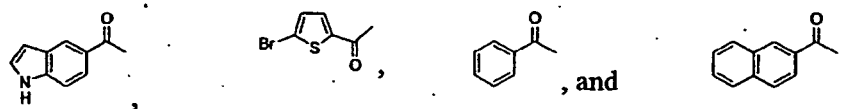
- (1) H,
- (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
- (3) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with aryl,
- (4) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heterocyclyl, and
- (5) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heteroaryl,

or R<sup>1L</sup> and R<sup>3L</sup> together with the atoms to which they are attached can form a substituted or unsubstituted-heterocyclic  
 ring, having from 3 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S.  
**[0069]** In another aspect, the present disclosure provides compounds of formula XI:

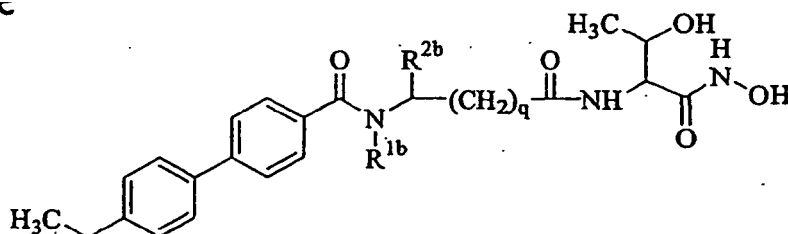


or stereoisomers, pharmaceutically acceptable salts, esters, and prodrugs thereof, wherein Y-X taken together, is selected from the group consisting of





[0070] In another aspect, the present disclosure provides compounds of formula XII:



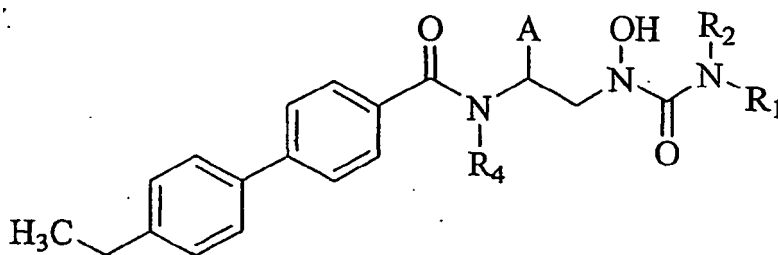
XII

or stereoisomers, pharmaceutically acceptable salts, esters, and prodrugs thereof, wherein  $R^{1b}$  and  $R^{2b}$  are independently selected from the group consisting of

- (1) H,
- (2) substituted or unsubstituted  $C_1$ - $C_6$ -alkyl,
- (3) substituted or unsubstituted  $C_2$ - $C_6$ -alkenyl,
- (4) substituted or unsubstituted  $C_2$ - $C_6$ -alkenyl,
- (5) substituted or unsubstituted aryl,
- (6) substituted or unsubstituted heterocyclyl,
- (7) substituted or unsubstituted heteroaryl,
- (8)  $C_1$ - $C_6$ -alkyl substituted with aryl,
- (9)  $C_1$ - $C_6$ -alkyl substituted with heterocyclyl, and
- (10)  $C_1$ - $C_6$ -alkyl substituted with heteroaryl;

q is an integer of 0-2;

[0071] In another aspect, the present disclosure provides compounds of formula XIII:



XIII

or stereoisomers, pharmaceutically acceptable salts, esters, and prodrugs thereof, wherein  $R_4$  is selected from the group consisting of

- (1) H,
- (2) substituted or unsubstituted  $C_1$ - $C_6$ -alkyl,
- (3)  $C_1$ - $C_6$ -alkyl substituted with aryl,
- (4)  $C_1$ - $C_6$ -alkyl substituted with heterocyclyl, and
- (5)  $C_1$ - $C_6$ -alkyl substituted with heteroaryl,

A is H or  $-\text{CH}(\text{CH}_3)\text{OH}$ ;

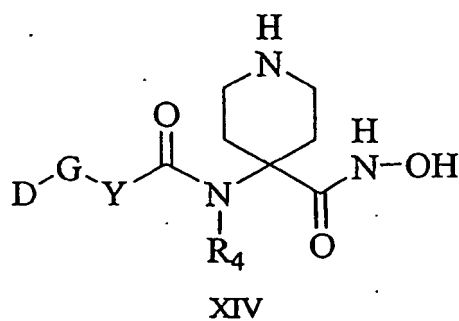
$R_1$  is H or substituted or unsubstituted  $C_1$ - $C_6$ -alkyl;

$R_2$  is selected from the group consisting of

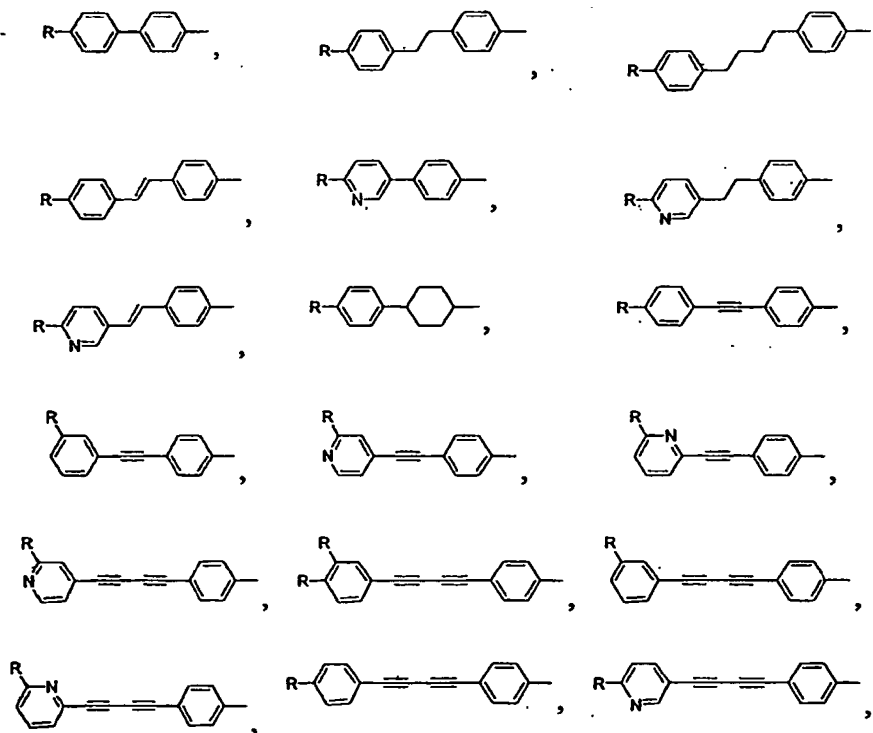
- (1) H,  
 (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,  
 (3) substituted or unsubstituted aryl,  
 (4) substituted or unsubstituted heterocyclyl,  
 (5) substituted or unsubstituted heteroaryl,  
 (6) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with aryl,  
 (7) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heterocyclyl,  
 (8) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heteroaryl,

or R<sup>1</sup> and R<sup>2</sup> together with the N atom to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 10 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S.

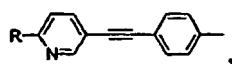
**[0072]** In another aspect, the present disclosure provides compounds of formula XIV:



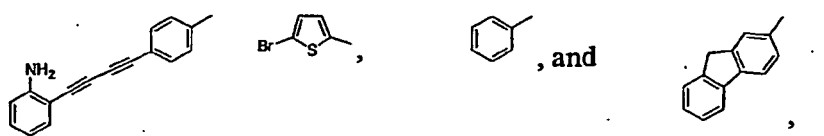
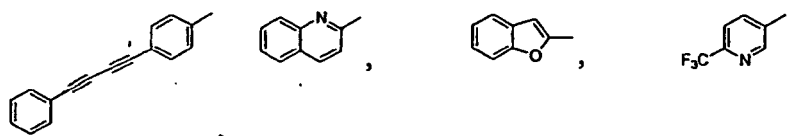
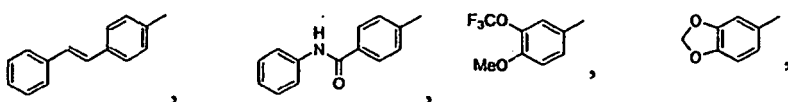
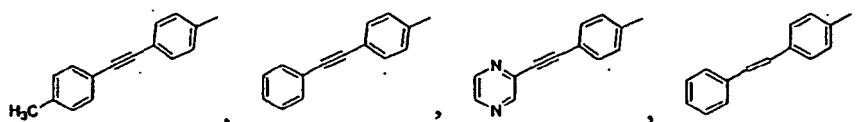
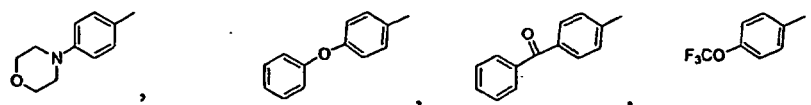
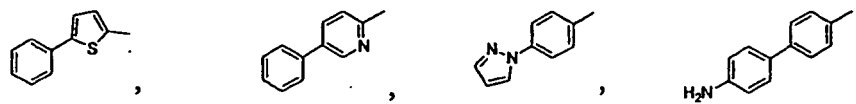
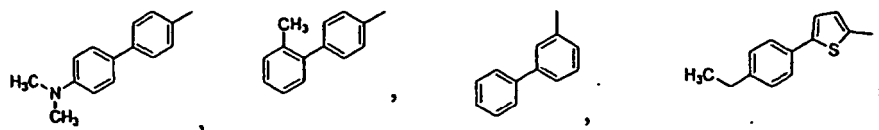
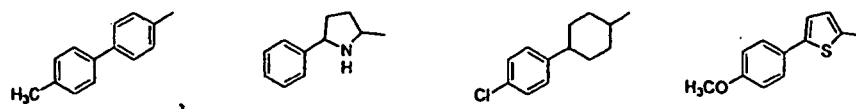
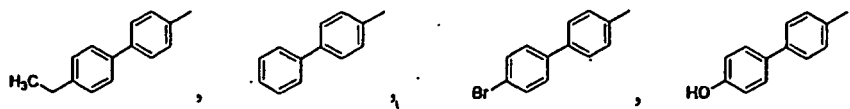
or stereoisomers, pharmaceutically acceptable salts, esters, and prodrugs thereof, wherein D-G-Y taken together is selected from the group consisting of



and



5 or



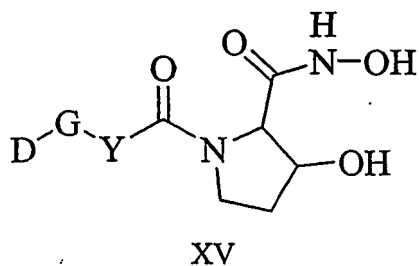
Wherein

R is selected from the group consisting of -CH<sub>3</sub>, -C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>OH, -OH, -OCH<sub>3</sub>, -OC<sub>2</sub>H<sub>5</sub>, OCF<sub>3</sub>, -CN, NO<sub>2</sub>, -CO<sub>2</sub>H, -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, NH<sub>2</sub>, F, -Cl, -Br, -CF<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -NHSO<sub>2</sub>CH<sub>3</sub>, and -NHCOCH<sub>3</sub>; R<sub>4</sub> is selected from the group

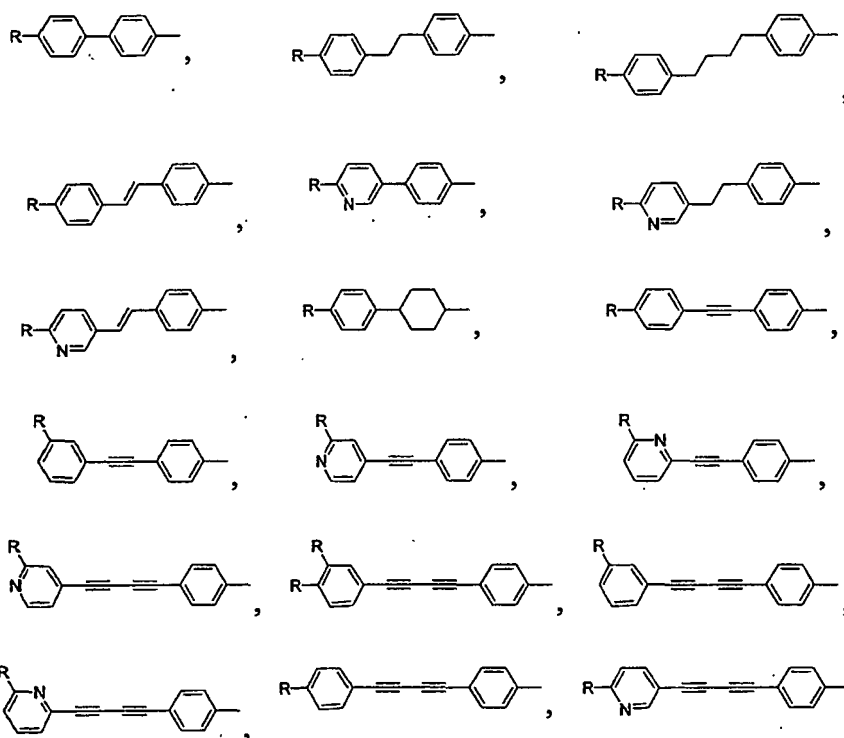
consisting of

- (1) H,
- (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
- (3) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with acryl,
- (4) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heterocyclyl, and
- (5) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heteroaryl.

**[0073]** In another aspect, the present disclosure provides compounds of formula XV:



or stereoisomers, pharmaceutically acceptable salts, esters, and prodrugs thereof, wherein D-G-Y taken together, is selected from the group consisting of

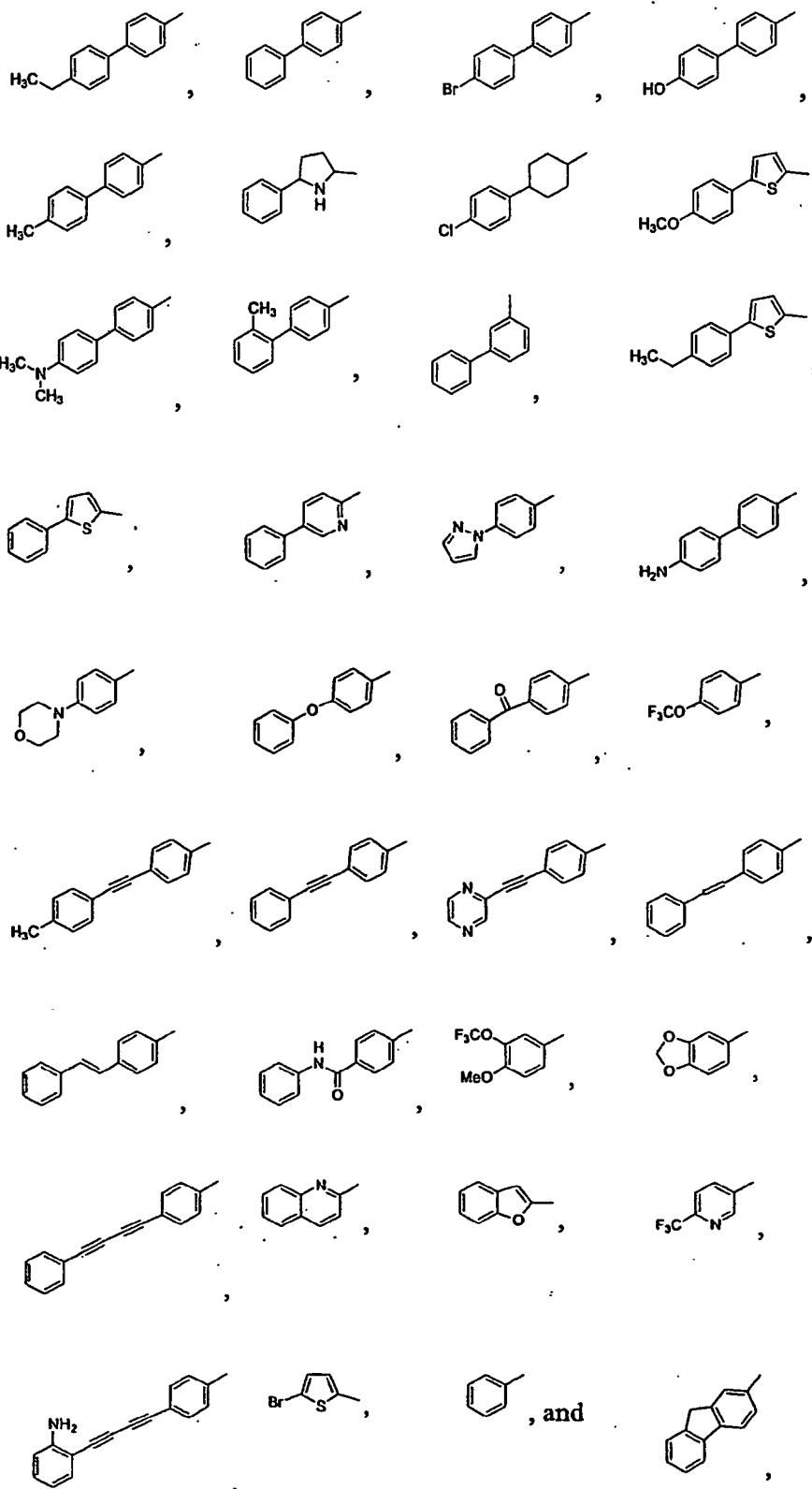


and



or

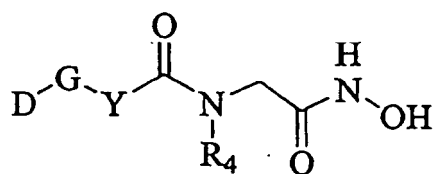




Wherein

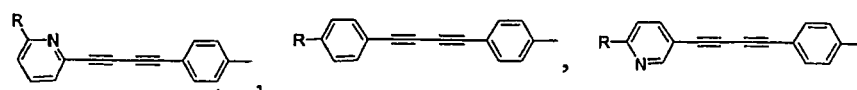
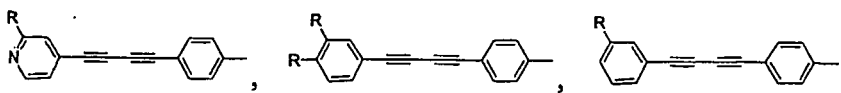
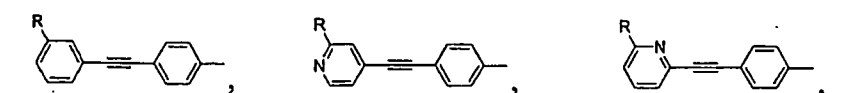
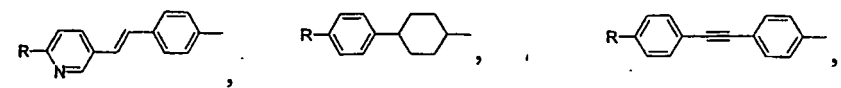
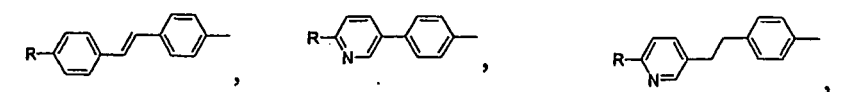
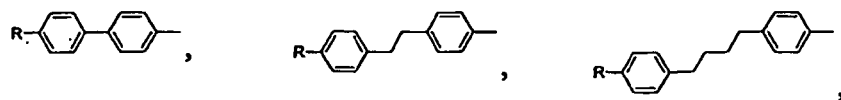
R is selected from the group consisting of -CH<sub>3</sub>, -C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>OH, -OH, -OCH<sub>3</sub>, -OC<sub>2</sub>H<sub>5</sub>, -OCF<sub>3</sub>, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>H, -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, -NH<sub>2</sub>, -F, -Cl, -Br, -CF<sub>3</sub>, N(CH<sub>3</sub>)<sub>2</sub>, -NHSO<sub>2</sub>CH<sub>3</sub>, and -NHCOCH<sub>3</sub>;

[0074] In another aspect, the present disclosure provides compounds of formula XVI:

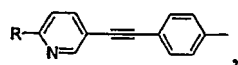


XVI

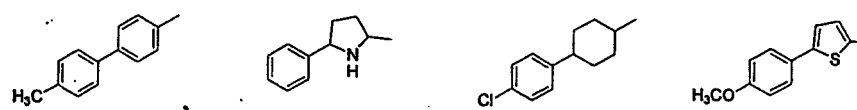
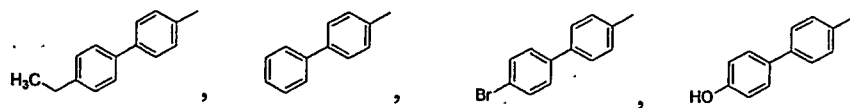
or stereoisomers, pharmaceutically acceptable salts, esters, and prodrugs thereof, wherein D-G-Y taken together, is selected from the group consisting of



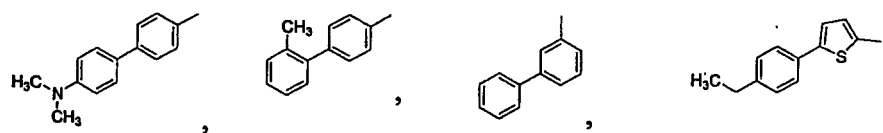
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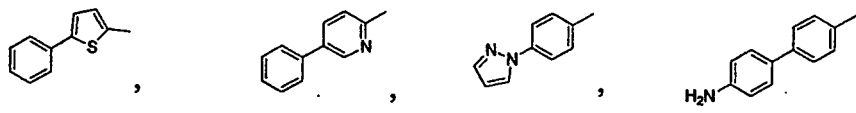
or



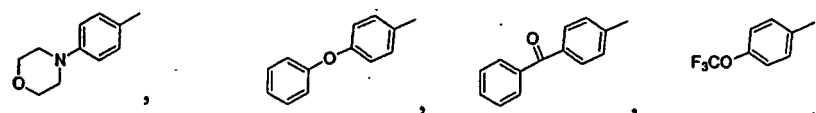
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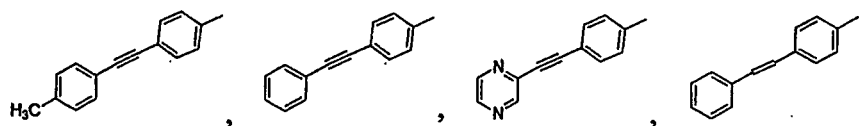
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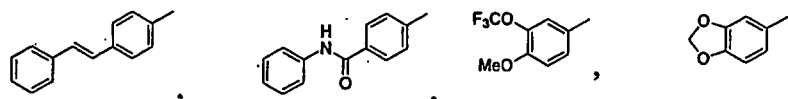
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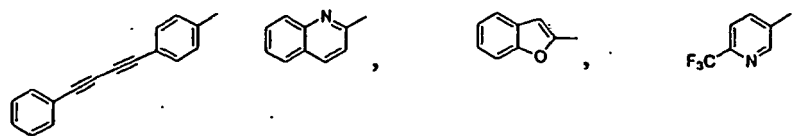
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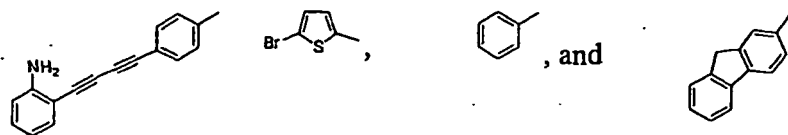
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Wherein

R is selected from the group consisting of -CH<sub>3</sub>, -C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>OH, -OH, -OCH<sub>3</sub>, -OC<sub>2</sub>H<sub>5</sub>, OCF<sub>3</sub>, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>H, -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, -NH<sub>2</sub>, -F, -Cl, -Br, -CF<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -NHSO<sub>2</sub>CH<sub>3</sub>, and NHCOCH<sub>3</sub>;

R<sub>4</sub> is selected from the group consisting of

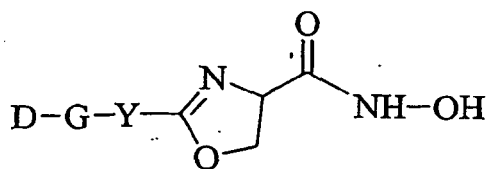
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- (1) H,
- (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
- (3) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with aryl,
- (4) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heterocyclyl, and
- (5) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heteroaryl;

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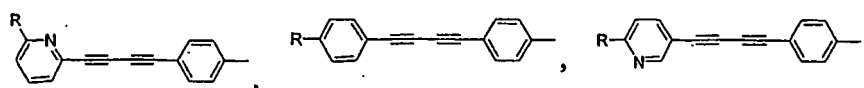
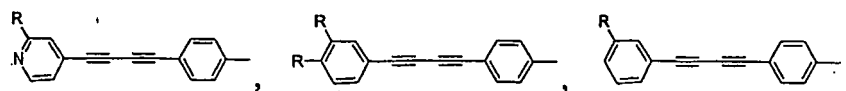
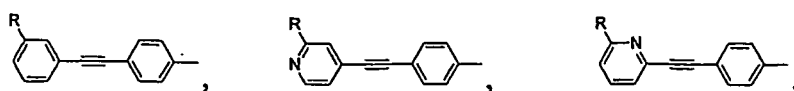
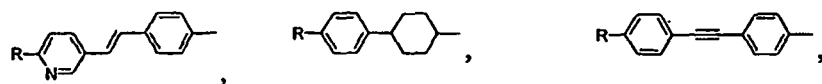
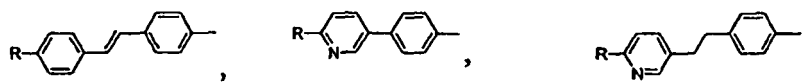
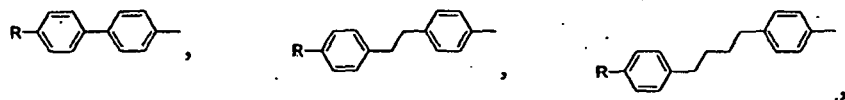
**[0075]** In another aspect, the present disclosure provides compounds of formula XVII:

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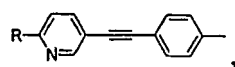


XVII

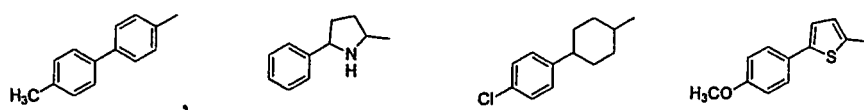
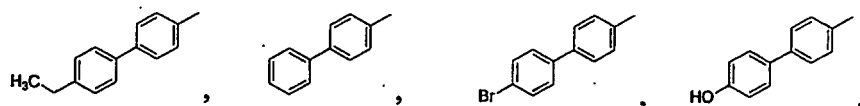
or stereoisomers, pharmaceutically acceptable salts, esters, and prodrugs thereof, wherein D-G-Y taken together, is selected from the group consisting of

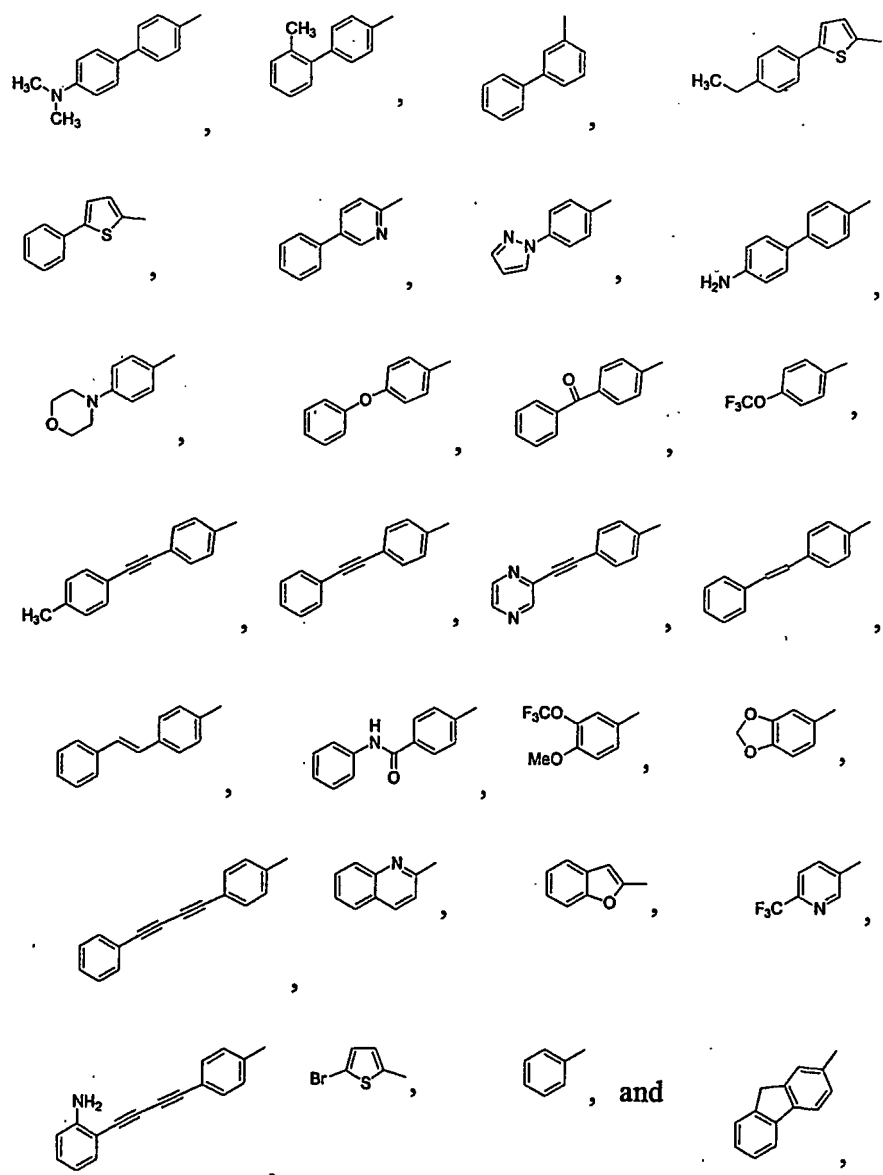


and



or





Wherein

R is selected from the group consisting of -CH<sub>3</sub>, -C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>OH, -OH, -OCH<sub>3</sub>, -OC<sub>2</sub>H<sub>5</sub>, -OCF<sub>3</sub>, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>H, -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, -NH<sub>2</sub>, -F, -Cl, -Br, -CF<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -NHSO<sub>2</sub>CH<sub>3</sub>, and -NHCOCH<sub>3</sub>;

[0076] In one aspect, the invention provides compounds for use in inhibiting a deacetylase enzyme in a gram-negative bacteria, thereby affecting bacterial growth said use comprising administering to a patient in need of such inhibition a compound of formula II, VI or VIII.

[0077] In another aspect, the invention provides compound for use in inhibiting LpxC, thereby modulating the virulence of a bacterial infection, said use comprising administering to a patient in need of such inhibition a compound of formula II, VI or VIII.

[0078] In some embodiments of inhibiting LpxC using a compound of formula II, VI or VIII, the IC<sub>50</sub> value of the compound is less than or equal to 10 μM with respect to LpxC. In other such embodiments, the IC<sub>50</sub> value is less than or equal to 1 μM, is less than or equal to 0.1 μM, is less than or equal to 0.050 μM, is less than or equal to 0.030 μM, is less than or equal to 0.025 μM, or is less than or equal to 0.010 μM.

[0079] In one aspect of the invention compounds for use in treating a subject are provided, said use comprising administering to the subject an antibacterially effective amount of a compound of formula II, VI or VIII together with a pharmaceutically acceptable carrier is provided. In a preferred embodiment of the invention the subject is a mammal and some embodiments, a human.

[0080] In another aspect, the invention provides compounds for use in a method of administering an inhibitory amount of a compound of formula II, VI or VII to fermentative or non-fermentative gram-negative bacteria. In a preferred em-

bodiment of the method of administering an inhibitory amount of a compound of formula II, VI or VIII to fermentative or non-fermentative gram-negative bacteria, the gram-negative bacteria are selected from the group consisting of *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *Alcaligenes xylosoxidans*, *Acinetobacter*, *Enterobacteriaceae*, *Haemophilus*, *Neisseria* species.

**[0081]** In another embodiment, the invention provides compounds for use in a method of administering an inhibitory amount of a compound of formula II, VI or VIII to gram-negative bacteria, such as *Enterobacteriaceae* that is selected from the group consisting of organisms such as *Serratia*, *Proteus*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Providencia*, *Morganella*, *Cedecea*, and *Edwardsiella* species and *Escherichia coli*.

**[0082]** Another embodiment of the invention provides a pharmaceutical composition comprising an effective amount of a compound of Formula II, VI or VIII with a pharmaceutically acceptable carrier thereof.

**[0083]** Pharmaceutical formulations according to the present invention are provided which include any of the compounds described above in combination with a pharmaceutically acceptable carrier.

**[0084]** Another embodiment of the invention provides compounds for use in a method of co-administering the compound of formula II, VI or VIII with other therapeutic agents that are selected for their particular usefulness against the condition that is being treated.

**[0085]** For example, the compound of formula II, VI or VIII is useful in combination with other anti-bacterial agents. The compound of formula II, VI or VIII augments the sensitivity of gram-negative bacteria to existing classes of antibiotics. Combinations of the presently disclosed compounds with other anti-bacterial agents are within the scope of the invention. Such anti-bacterial agents include erythromycin, rifampicin, Nalidixic acid, carbenicillin, bacitracin, cycloserine, fosfomycin, and vancomycin.

**[0086]** A further aspect of the invention is LpxC inhibitors according to the claims for use in the treatment of an infection, particularly a bacterial infection. A bacterial infection treated with the compounds of the invention can be a primary infection or a co-infection caused by a species of bacteria and one or more additional infectious agents selected from the group consisting of bacteria, virus, parasite and fungus.

**[0087]** The term "treating", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

**[0088]** The compounds of the invention can be used for treating conditions caused by the bacterial production of endotoxin and, in particular, by gram-negative bacteria and bacteria that use LpxC in the biosynthesis of lipopolysaccharide (LPS) or endotoxin.

**[0089]** The compounds of the invention also are useful in the conditions that are caused or exacerbated by the bacterial production of lipid A and LPS or endotoxin, such as sepsis, septic shock, systemic inflammation, localized inflammation, chronic obstructive pulmonary disease (COPD) and acute exacerbations of chronic bronchitis (AECB). For these conditions, treatment includes the administration of a compound of the invention, or a combination of compounds of the invention, optionally with a second agent wherein the second agent is a second antibacterial agent or a second non-antibacterial agent.

**[0090]** For sepsis, septic shock, systemic inflammation, localized inflammation, chronic obstructive pulmonary disease (COPD) and acute exacerbations of chronic bronchitis (AECB), preferred second non-antibacterial agents include anti-endotoxins including endotoxin receptor-binding antibodies, endotoxin-binding antibodies, anti-CD14-binding protein antibodies, antilipopolysaccharide-binding protein antibodies and tyrosine kinase inhibitors.

**[0091]** In treatment of serious or chronic respiratory tract infections, the compounds of the present invention may also be used with second non-antibacterial agents administered via inhalation. Preferred non-antibacterial agents used in this treatment include anti-inflammatory steroids, non-steroidal anti-inflammatory agents, bronchodilators, mucolytics, anti-asthma therapeutics and lung fluid surfactants. In particular, the non-antibacterial agent may be selected from a group consisting of albuterol, salbuterol, budesonide, beclomethasone, dexamethasone, nedocromil, beclomethasone, fluticasone, flunisolide, triamcinolone, ibuprofen, rofecoxib, naproxen, celecoxib, nedocromil, ipratropium, metaproterenol, pirbuterol, salmeterol, bronchodilators, mucolytics, calfactant, beractant, poractant alfa, surfaxin and pulmozyme (also called dornase alfa).

**[0092]** The compounds of the invention can be used, alone or in combination with a second antibacterial agent for the treatment of a serious or chronic respiratory tract infection including serious lung and nosocomial infections such as those caused by *Enterobacter aerogenes*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Proteus mirabilis*, *Serratia marcescens*, *Stenotrophomonas maltophilia*, *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Acinetobacter calcoaceticus*, *Alcaligenes xylosoxidans*, *Flavobacterium meningosepticum*, *Providencia stuartii* and *Citrobacter freundii*, community lung infections such as those caused by *Haemophilus Influenzae*, *Legionella* species, *Moraxella catarrhalis*, *Branhamella catarrhalis*, *Enterobacter* species, *Acinetobacter* species, *Klebsiella* species, and *Proteus* species, and infections caused by other bacterial species such as *Neisseria* species, *Shigella* species, *Salmonella* species, *Helicobacter pylori*, *Vibrionaceae* and *Bordetella* species as well as the infections is caused by a *Brucella* species, *Francisella tularensis* and/or *Yersinia Pestis*.

**[0093]** When used for treating Gram-negative bacteria, the compounds of the present invention can be used to sensitize gram-negative bacteria to the effects of a second agent.

**[0094]** When the compounds of the present invention are used in combination with a second antibacterial agent, examples of antibacterial agents may be selected from the following groups:

- (1) Macrolides or ketolides such as erythromycin, azithromycin, clarithromycin and telithromycin;
- (2) Beta-lactams including penicillin, cephalosporin, and carbapenems such as carbapenem, imipenem, and meropenem;
- (3) Monobactams such as penicillin G, penicillin V, methicillin, oxacillin, cloxacillin, dicloxacillin, nafcillin, ampicillin, amoxicillin, carbenicillin, ticarcillin, mezlocillin, piperacillin, azlocillin, temocillin, cephalothin, cephapirin, cephradine, cephaloridine, cefazolin, cefamandole, cefuroxime, cephalexin, cefprozil, cefaclor, loracarbef, cefoxitin, cefmetazole, cefotaxime, ceftizoxime, ceftriaxone, cefoperazone, ceftazidime, cefixime, cefpodoxime, ceftibuten, cefdinir, cefpirome, cefepime, and astreonam;
- (4) Quinolones such as nalidixic acid, oxolinic acid, norfloxacin, pefloxacin, enoxacin, ofloxacin, levofloxacin, ciprofloxacin, temafloxacin, lomefloxacin, fleroxacin, grepafloxacin, sparfloxacin, trovafloxacin, clinafloxacin, gatifloxacin, moxifloxacin, sitafloxacin, ganefloxacin, gemifloxacin and pazufloxacin;
- (5) Antibacterial sulfonamides and antibacterial sulphanilamides, including para-aminobenzoic acid, sulfadiazine, sulfisoxazole, sulfamethoxazole and sulfathalidine;
- (6) Aminoglycosides such as streptomycin, neomycin, kanamycin, paromycin, gentamicin, tobramycin, amikacin, netihnicin, spectinomycin, sisomicin, dibekalin and isepamicin;
- (7) Tetracyclines such as tetracycline, chlortetracycline, demeclocycline, minocycline, oxytetracycline, methacycline, doxycycline;
- (8) Rifamycins such as rifampicin (also called rifampin), rifapentine, rifabutin, bezoxazinorifamycin and rifaximin;
- (9) Lincosamides such as lincomycin and clindamycin;
- (10) Glycopeptides such as vancomycin and teicoplanin;
- (11) Streptogramins such as quinupristin and daflopristin;
- (12) Oxazolidinones such as linezolid;
- (13) Polymyxin, colistin and colymycin;
- (14) Trimethoprim and bacitracin.

**[0095]** The second antibacterial agent may be administered in combination with the compounds of the present inventions wherein the second antibacterial agent is administered prior to, simultaneously, or after the compound or compounds of the present invention. When simultaneous administration of a compound of the invention with a second agent is desired and the route of administration is the same, then a compound of the invention may be formulated with a second agent into the same dosage form. An example of a dosage form containing a compound of the invention and a second agent is a tablet or a capsule.

**[0096]** When used for treating a serious or chronic respiratory tract infections, the compounds of the invention may be used alone or in combination with a second antibacterial agent administered via inhalation. In the case of inhalation, a preferred second antibacterial agent is selected from a group consisting of tobramycin, gentamicin, aztreonam, ciprofloxacin, polymyxin, colistin, colymycin, azithromycin and clarithromycin.

## Pharmaceutical Compositions

**[0097]** Pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers. As used

herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials that can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such as propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator. The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray, or a liquid aerosol or dry powder formulation for inhalation.

**[0098]** Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

**[0099]** Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

**[0100]** The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

**[0101]** In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form may be accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations may also be prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissues.

**[0102]** Compositions for rectal or vaginal administration are preferably suppositories that can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

**[0103]** Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, acetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

**[0104]** Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules



using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols.

**[0105]** The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

**[0106]** Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols.

**[0107]** The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

**[0108]** Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulations and ear drops are also contemplated as being within the scope of this invention.

**[0109]** The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

**[0110]** Compositions of the invention may also be formulated for delivery as a liquid aerosol or inhalable dry powder. Liquid aerosol formulations may be nebulized predominantly into particle sizes that can be delivered to the terminal and respiratory bronchioles where bacteria reside in patients with bronchial infections, such as chronic bronchitis and pneumonia. Pathogenic bacteria are commonly present throughout airways down to bronchi, bronchioli and lung parenchyma, particularly in terminal and respiratory bronchioles. During exacerbation of infection, bacteria can also be present in alveoli. Liquid aerosol and inhalable dry powder formulations are preferably delivered throughout the endobronchial tree to the terminal bronchioles and eventually to the parenchymal tissue.

**[0111]** Aerosolized formulations of the invention may be delivered using an aerosol forming device, such as a jet, vibrating porous plate or ultrasonic nebulizer, preferably selected to allow the formation of aerosol particles having with a mass medium average diameter predominantly between 1 to 5  $\mu\text{m}$ . Further, the formulation preferably has balanced osmolarity ionic strength and chloride concentration, and the smallest aerosolizable volume able to deliver effective dose of the compounds of the invention to the site of the infection. Additionally, the aerosolized formulation preferably does not impair negatively the functionality of the airways and does not cause undesirable side effects.

**[0112]** Aerosolization devices suitable for administration of aerosol formulations of the invention include, for example; jet, vibrating porous plate, ultrasonic nebulizers and energized dry powder inhalers, that are able to nebulize the formulation of the invention into aerosol particle size predominantly in the size range from 1-5  $\mu\text{m}$ . Predominantly in this application means that at least 70% but preferably more than 90% of all generated aerosol particles are 1 to 5  $\mu\text{m}$  range. A jet nebulizer works by air pressure to break a liquid solution into aerosol droplets. Vibrating porous plate nebulizers work by using a sonic vacuum produced by a rapidly vibrating porous plate to extrude a solvent droplet through a porous plate. An ultrasonic nebulizer works by a piezoelectric crystal that shears a liquid into small aerosol droplets. A variety of suitable devices are available, including, for example, AeroNeb and AeroDose vibrating porous plate nebulizers (AeroGen, Inc., Sunnyvale, California), Sidestream7 nebulizers (Medic-Aid Ltd., West Sussex, England), Pari LC7 and Pari LC Star7 jet nebulizers (Pari Respiratory Equipment, Inc., Richmond, Virginia), and Aerosonic (DeVilbiss Medizinische Produkte (Deutschland) GmbH, Heiden, Germany) and UltraAire7 (Omron Healthcare, Inc., Vernon Hills, Illinois) ultrasonic nebulizers.

**[0113]** Compounds of the invention may also be formulated for use as topical powders and sprays that can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

**[0114]** Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

**[0115]** According to the methods of treatment of the present disclosure, bacterial infections are treated or prevented in a patient such as a human or lower mammal by administering to the patient a therapeutically effective amount of a compound of the invention, in such amounts and for such time as is necessary to achieve the desired result. By a "therapeutically effective amount" of a compound of the invention is meant a sufficient amount of the compound to treat bacterial infections, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

**[0116]** The total daily dose of the compounds of this invention administered to a human or other mammal in single or in divided doses can be in amounts, for example, from 0.01 to 50 mg/kg body weight or more usually from 0.1 to 25 mg/kg body weight. Single dose compositions may contain such amounts or submultiples thereof to make up the daily dose. In general, treatment regimens according to the present disclosure comprise administration to a patient in need of such treatment from about 10 mg to about 2000 mg of the compound(s) of this invention per day in single or multiple doses.

**[0117]** Methods of formulation are well known in the art and are disclosed, for example, in Remington: The Science and Practice of Pharmacy, Mack Publishing Company, Easton, Pa., 19th Edition (1995). Pharmaceutical compositions for use in the present invention can be in the form of sterile, non-pyrogenic liquid solutions or suspensions, coated capsules, suppositories, lyophilized powders, transdermal patches or other forms known in the art.

**[0118]** A "kit" as used in the instant application includes a container for containing the pharmaceutical compositions and may also include divided containers such as a divided bottle or a divided foil packet. The container can be in any conventional shape or form as known in the art that is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a resealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle that is in turn contained within a box.

**[0119]** An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process, recesses are formed in the plastic foil. The recesses have the size and shape of individual tablets or capsules to be packed or may have the size and shape to accommodate multiple tablets and/or capsules to be packed. Next, the tablets or capsules are placed in the recesses accordingly and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil that is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are individually sealed or collectively sealed, as desired, in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

**[0120]** It may be desirable to provide a written memory aid, where the written memory aid is of the type containing information and/or instructions for the physician, pharmacist or other health care provider, or subject, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen that the tablets or capsules so specified should be ingested or a card that contains the same type of information. Another example of such a memory aid is a calendar printed on the card e.g., as follows "First Week, Monday, Tuesday, ..." etc ... "Second Week, Monday, Tuesday, ..." etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several tablets or capsules to be taken on a given day. When the kit contains separate compositions, a daily dose of one or more compositions of the kit can consist of one tablet or capsule while a daily dose of another one or more compositions of the kit can consist of several tablets or capsules.

**[0121]** Another specific embodiment of a kit is a dispenser designed to dispense the daily doses one at a time in the order of their intended use. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter, that indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal that, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

**[0122]** The kits of the present invention may also include, in addition to LpxC inhibitors, one or more additional phar-

maceutically active compounds. Preferably, the additional compound is another LpxC inhibitor or another compound useful to bacterial infections. The additional compounds may be administered in the same dosage form as the LpxC inhibitor or in different dosage forms. Likewise, the additional compounds can be administered at the same time as the LpxC inhibitor or at different times.

**[0123]** Compositions of the present compounds may also be used in combination with other known anti-bacterial agents of similar spectrum to (1) synergistically enhance treatment of severe Gram-negative infections covered by the spectrum of this compound or (2) add coverage in severe infections in which multiple organisms are suspected in which another agent of a different spectrum may be required in addition to this compound. Potential agents include members of the aminoglycosides, penicillins, cephalosporins, fluoroquinolones, macrolides, glycopeptides, lipopeptides and oxazolidinones. The treatment can involve administering a composition having both active agents or administration of the inventive compounds followed by or preceded by administration of an additional active antibacterial agent.

## Characterization and Purification Methods

**[0124]** Referring to the examples that follow, compounds of the present invention were characterized by high performance liquid chromatography (HPLC) using a Waters Millenium chromatography system with a 2690 Separation Module (Milford, Massachusetts). The analytical columns were Alltima C-18 reversed phase, 4.6 x 250 mm from Alltech (Deerfield, Illinois). A gradient elution was used, typically starting with 5% acetonitrile/95% water and progressing to 100% acetonitrile over a period of 40 minutes. All solvents contained 0.1 % trifluoroacetic acid (TFA). Compounds were detected by ultraviolet light (UV) absorption at either 220 or 254 nm. HPLC solvents were from Burdick and Jackson (Muskegan, Michigan), or Fisher Scientific (Pittsburg, Pennsylvania). In some instances, purity was assessed by thin layer chromatography (TLC) using glass or plastic backed silica gel plates, such as, for example, Baker-Flex Silica Gel 1B2-F flexible sheets. TLC results were readily detected visually under ultraviolet light, or by employing well known iodine vapor and other various staining techniques.

**[0125]** Mass spectrometric analysis was performed on one of two LCMS instruments: a Waters System (Alliance HT HPLC and a Micromass ZQ mass spectrometer; Column: Eclipse XDB-C18, 2.1 x 50 mm; solvent system: 5-95% (or 35-95%, or 65-95% or 95-95%) acetonitrile in water with 0.05%TFA; flow rate 0.8 mL/min; molecular weight range 500-1500; cone Voltage 20 V; column temperature 40°C) or a Hewlett Packard System (Series 1100 HPLC; Column: Eclipse XDB-C18, 2.1 x 50 mm; solvent system: 1-95% acetonitrile in water with 0.05%TFA; flow rate 0.4 mL/min; molecular weight range 150-850; cone Voltage 50 V; column temperature 30°C). All masses are reported as those of the protonated parent ions.

**[0126]** GCMS analysis was performed on a Hewlett Packard instrument (HP6890 Series gas chromatograph with a Mass Selective Detector 5973; injector volume: 1 µL; initial column temperature: 50°C; final column temperature: 250°C; ramp time: 20 minutes; gas flow rate: 1 mL/min; column: 5% phenyl methyl siloxane, Model #HP 190915-443, dimensions: 30.0 m x 25 m x 0.25 m).

**[0127]** Nuclear magnetic resonance (NMR) analysis was performed with a Varian 300 Mhz NMR (Palo Alto, California). The spectral reference was either TMS or the known chemical shift of the solvent. Some compound samples were run at elevated temperatures (e.g. 75°C) to promote increased sample solubility.

**[0128]** The purity of some of the invention compounds was assessed by elemental analysis (Desert Analytics, Tuscon, Arizona)

**[0129]** Melting points were determined on a Laboratory Devices Mel-Temp apparatus (Holliston, Massachusetts).

**[0130]** Preparative separations were carried out using a Flash 40 chromatography system and KP-Sil, 60A (Biotage, Charlottesville, Virginia), or by flash column chromatography using silica gel (230-400 mesh) packing material, or by HPLC using a C-18 reversed phase column. Typical solvents employed for the Flash 40 Biotage system and flash column chromatography were dichloromethane, methanol, ethyl acetate, hexane, acetone, aqueous hydroxylamine and triethyl amine. Typical solvents employed for the reverse phase HPLC were varying concentrations of acetonitrile and water with 0.1 % trifluoroacetic acid.

**[0131]** Compounds of the present invention can be readily synthesized using the methods described herein, or other methods, that are well known in the art. For example, the synthesis of hydroxamic acids or similar scaffolds having a wide variety of substituents are comprehensively reviewed in Kline T, Andersen NH, Harwood EA, Bowman J, Malanda A, Endsley S, Erwin AL, Doyle M, Fong S, Harris AL, Mendelsohn B, Mdluli K, Raetz CR, Stover CK, Witte PR, Yabannavar A, Zhu S., "Potent, novel in vitro inhibitors of the *Pseudomonas aeruginosa* deacetylase LpxC," J Med Chem 2002 Jul 4;45(14):3112-29; Patchett, A. A., Nargund, R.; Chen, M.-H., Nishi, H. R., U. S. Patent 5,925,659, 1999; Pirrung, M. C., Chau, J. H., "A Convenient Procedure for the Preparation of Amino Acid Hydroxamates from Esters," J. Org. Chem. 1995, 60, 8084-8085; Nhu, K., Patel, D. V., "A New and Efficient Solid Phase Synthesis of Hydroxamic Acids," J. Org. Chem. 1997, 62, 7088-7089; Patel, D., Nhu, K., "Methods for Solid-phase Synthesis of Hydroxylamine Compounds and Derivatives, and Combinatorial Libraries Thereof," PCT WO 98/18754, 1998, Mellor, S. L., McGuire, C., Chan, W. C., "N-Fmoc-aminoxy-2-chlorotriyl Polystyrene Resin: A Facile Solid-phase Methodology for the Synthesis of Hydroxamic

Acids," *Tetrahedron Lett.*, 1997, 38, 3311-3314; Khan, S. I., Grinstaff, M. W., "A Facile and Convenient Solid-phase Procedure for Synthesizing Nucleoside Hydroxamic Acids," *Tetrahedron Lett.*, 1998, 39, 803,1-8034; Zhang, Y., Li, D., Houtman, J. C., Witiak, D. T., Seltzer, J., Bertics, P. J., Lauhon, C. T., "Design, Combinatorial Chemical Synthesis, and in vitro Characterization of Novel Urea Based Gelatinase Inhibitors," *Bioorg. Med. Chem. Lett.*, 1999, 9, 2823-2826; Ito, Y., Inubushi, Y., Zenbayashi, M., Tomita, S., Saegusa, T., "Synthetic Reactions by Complex Catalysts. XXXI, A Novel and Versatile Method of Heterocycle Synthesis," *J. Am. Chem. Soc.*, 1973, 95, 4447-4448; Ito, Y., Ito, I., Hirao, T., Saegusa, T., "Synthetic Reactions by Complex Catalysts XXXV," *Syn. Commun.* 1974, 4, 97-103; Witte, H., Seliger, W., "Cyclische Imidsaurester aus Nitrilen und Aminoalkoholen," *Liebigs Ann. Chem.*, 1974, 996-1009; Pattenden, G., Thom. S. M., "Naturally Occurring Linear Fused Thiazoline-Thiazole Containing Metabolites: Total Synthesis of (-) Didehydromirabazole A, a Cytotoxic Alkaloid from Blue-Green Algae," *J. Chem. Soc. Perkin Trans 1*, 1993, 1629-1636; Boyce, R J., Mulqueen, G. C., Pattenden, G., "Total Synthesis of Thiagazole, A Novel Naturally Occurring HIV-1 Inhibitor from *Polyangium* sp.," *Tetrahedron*, 1995, 51, 7321-7330; Galeotti, N., Plagnes, E., Jouin, P., "Synthesis of Peptidyl Aldehydes from Thiazolines," *Tetrahedron Lett.* 1997, 38, 2459-2462; Charette, A. B., Chua, P., "Mild Method for the Synthesis of Thiazolines from Secondary and Tertiary Amides," *J. Org. Chem.*, 1998, 63, 908-909; Bergeron, R. J., Wiegand, J., McManis, J. S., McCosar, B.H., Weimar, W. R., Brittenham, G. M., Smith, R. E., "Effects of C-4 Stereochemistry and C-4' Hydroxylation on the Iron Clearing Efficiency and Toxicity of Desferrithiocin Analogues," *J. Med. Chem.* 1999, 42, 2432-2440; Raman, P., Razavik H., Kelly, J. W., "Titanium (IV)-mediated Tandem Deprotection-cyclodehydration of Protected Cysteine N-Amides: Biomimetic Synthesis of Thiazoline- and Thiazole-containing Heterocycles," *Org. Lett.*, 2000, 2, 3289-3292; Fernandez, X., Fellous, R., Dunach, E., "Novel Synthesis of 2-Thioazolines," *Tetrahedron Lett.*, 2000, 41, 3381-3384. Wipf, P., Miller, C. P., Venkatraman, S., Fritch, P., "C. Thiols of Oxazolinones: A New, Selective Method for the Direct Conversion of Peptide Oxazolinones into. Thiazolines," *Tetrahedron Lett.*, 1995, 36, 6395-6398

**[0132]** The synthesis of other non-hydroxamates compounds or more generally zinc binding groups are reviewed in Pirrung, M. C., Tumey, L. N., Raetz, C. R. H., Jackman, J. E., Snehalatha, K., McClerren, A. L., Fierke, C. A., Gantt, S. L., Rusche, K. M., "Inhibition of the Antibacterial Target UDP-(3-O-acyl)-N-acetylglucosamine Deacetylase (LpxC): Isoxazoline Zinc Amidase Inhibitors Bearing Diverse Metal Binding Groups," *Journal of Medicinal Chemistry* (2002), 45 (19), 4359-4370; Jackman, J. E., Fierke, C. A., Tumey, L. N., Pirrung, M., Uchiyama, T., Tahir, S. H., Hindsgaul, O., Raetz, C. R. H., "Antibacterial agents that target lipid A biosynthesis in gram-negative bacteria: inhibition of diverse UDP-3-O-(R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylases by substrate analogs containing zinc binding motifs," *Journal of Biological Chemistry* (2000), 275(15), 11002-11009; Brooks, C. D. W., Summers, J. B., "Modulators of Leukotriene Biosynthesis and Receptor Activation," *Journal of Medicinal Chemistry* (1996), 39(14), 2629-2654; Jeng, A. Y., De Lombaert, S., "Endothelin converting enzyme inhibitors," *Current Pharmaceutical Design* (1997), 3(6), 597-614; Zask, A., Levin, J. I., Killar, L. M., Skotnicki, J. S., "Inhibition of matrix metalloproteinases: structure based design," *Current Pharmaceutical Design* (1996), 2(6), 624-661; Skotnicki, J. S., DiGrandi, M. J., Levin, J. I., Chemical and Screening Sciences, Wyeth Research, New York, NY, USA. *Current Opinion in Drug Discovery & Development* (2003), 6(5), 742-759. The foregoing may be better understood by reference to the following examples, that are presented for illustration.

## EXAMPLES

**[0133]** The following are abbreviations used in the examples:

AcOH: Acetic acid

aq: Aqueous

ATP: Adenosine triphosphate

Boc: tert-butoxycarbonyl

Boc-Thr(OBn)-OH 3-(R)-Benzyloxy-2-(S)-tert-butoxycarbonylamino-butyric acid.

DAP or Damp : Diaminopropionate

DCM: 4-(Dicyanomethylene)-2-methyl-6-(4-dimethylaminostyryl)-4H-pyran

DEAD: Diethyl azodicarboxylate

DIEA: Diisopropylethylamine

	DME:	1,2-dimethoxyethane
	DMF:	N,N-Dimethylformamide
5	DMSO:	Dimethyl sulfoxide
	DPPA:	Diphenyl phosphoryl azide
10	Et <sub>3</sub> N:	Triethylamine
	EDC:	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide
	EDCI:	1-(3-dimethylaminopropyl)3-ethylcarbodiimide
15	EtOAc:	ethyl acetate
	EtOH:	Ethanol
20	Fmoc:	9-fluorenylmethoxycarbonyl
	Gly-OH:	glycine
	HATU:	O-(7-azabenzotriazol-1-yl)-N,N,N'=tetramethyluronium hexafluorophosphate
25	HBTU:	2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
	Hex:	hexane
30	HOBt:	butyl alcohol
	HQBT:	1-Hydroxybenzotriazole
	HPLC:	High Pressure Liquid Chromatography
35	IC <sub>50</sub> value:	The concentration of an inhibitor that causes a 50 % reduction in a measured activity.
	iPrOH:	Isopropanol
40	LC/MS:	Liquid Chromatography/Mass Spectrometry
	LEMS:	Low Resolution Mass Spectrometry
	MeOH:	Methanol
45	NaOMe:	sodium methoxide
	nm:	Nanometer
50	NMP:	N-Methylpyrrolidone
	PPh <sub>3</sub> :	triphenyl phosphine
	RP-HPLC:	Reversed-phase high-pressure liquid chromatography
55	RT:	Room temperature
	sat:	Saturated

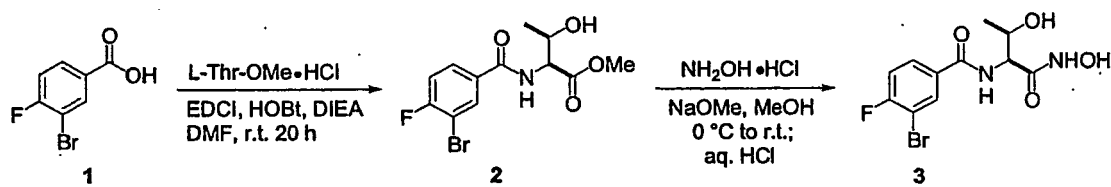
TEA:	Triethylamine
TFA:	Trifluoroacetic acid
5 THF:	Tetrahydrofuran
Thr:	Threonine
TLC:	Thin Layer Chromatography
10 Trt-Br:	Tert-butyl bromide

[0134] Nomenclature for the Example compounds was provided using ACD Name version 5.07 software (November 14, 2001) available from Advanced Chemistry Development, Inc. Some of the compounds and starting materials were named using standard IUPAC nomenclature.

### Synthesis of N-Aroyl Threonine Analogues and Formation of Hydroxamate

Example 1: Synthesis of 3-bromo-4-fluoro-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino) carbonyl]propyl)benzamide (3).

[0135]



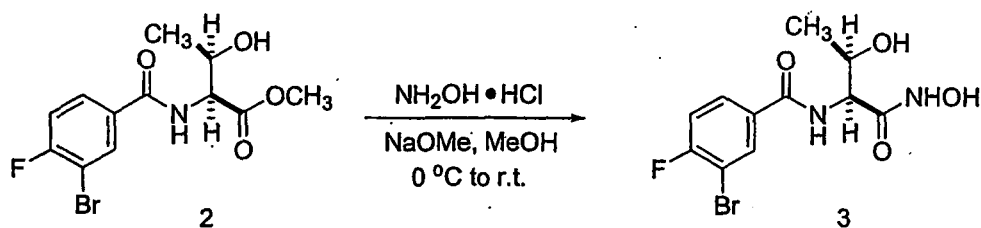
Reagent	MW	Eq.	g/ml	mmol
Benzoic acid (1)	219.02	1.0	2.152 g	9.83
L-Thr-OMe-HCl	169.61	1.2	1.968 g	11.6
EDCI	191.71	1.2	2.218 g	11.6
HOBt	135.13	1.1	1.410 g	10.4
DIEA	129.25	4.0	6.8 mL	39.0
DMF			60 mL	

### Preparation of (2S,3R)-2-(3-bromo-4-fluorobenzoylamino)-3-hydroxybutyric acid methyl ester (2)

[0136] Diisopropylethylamine (6.8 mL, 39.0 mmol) was added to a stirred solution of 3-bromo-4-fluorobenzoic acid **1** (2.152 g, 9.83 mmol), L-threonine methyl ester hydrochloride (1.968 g, 11.6 mmol), EDCI (2.218 g, 11.6 mmol) and HOBt (1.410 g, 10.4 mmol) in anhydrous DMF (60 mL) at 0 °C under N<sub>2</sub>. The solution was stirred at 0 °C for 1h and at room temperature for 20 h. The solution was diluted with EtOAc (300 mL) and washed with 1.0 M HCl (2 × 80 mL), saturated NaHCO<sub>3</sub> (2 × 80 mL), H<sub>2</sub>O (4 × 80 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to give a colorless syrup which solidified on standing to afford 3.280 g (100%) of (2S,3R)-2-(3-bromo-4-fluorobenzoylamino)-3-hydroxybutyric acid methyl ester **2** as a white solid, mp 73-74 °C. MS(ES+) m/z 333.9 (C<sub>12</sub>H<sub>13</sub>BrFNO<sub>4</sub>+H requires 334.00).

### Preparation of 3-bromo-4-fluoro-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl] propyl)benzamide (3)

[0137]

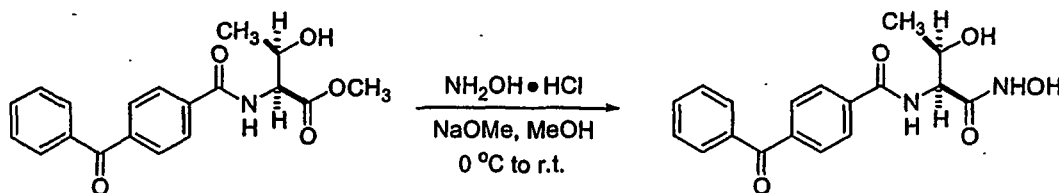


**[0138]** To a solution of hydroxylamine hydrochloride (66 mg, 0.95 mmol) in anhydrous MeOH (2.0 mL) at 0 °C under N<sub>2</sub> atmosphere was added sodium methoxide (25 wt% in MeOH, 360 mg, 1.67 mmol). A precipitate formed immediately and the cloudy white solution was stirred for 10 minutes at 0 °C. A solution of methyl (2S,3R)-2-[(3-bromo-4-fluorophenyl)carbonylamino]-3-hydroxybutanoate (**2**) (284 mg, 0.850 mmol) in MeOH (2.0 mL) was added and the reaction stirred 2 h at 0 °C and then warmed gradually to room temperature overnight (17 h total). Aqueous 1.0 M HCl (10 mL) was added and the solution extracted with 4:1 chloroform/isopropyl alcohol (4 × 20 mL). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give a pink foam. The crude solid was triturated with diethyl ether (2 × 8 mL) and dried in vacuo to give 3-bromo-4-fluoro-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide **3** as a white foam: mp 152-153 °C. R<sub>f</sub> (10:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH on silica gel) = 0.53.

## Preparation of Hydroxamates

### Example 2: Synthesis of 4-benzoyl-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino) carbonyl]propyl]benzamide

**[0139]**



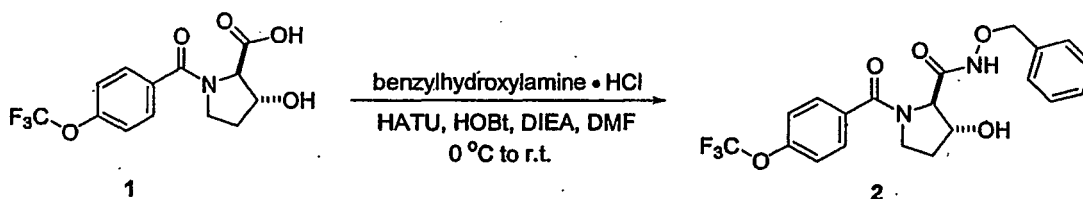
## Procedure:

**[0140]** To a solution of hydroxylamine hydrochloride (121 mg, 1.74 mmol) in anhydrous MeOH (2.0 mL) at 0 °C under N<sub>2</sub> atmosphere was added sodium methoxide (25 wt% in MeOH, 680 mg, 3.14 mmol). A precipitate was immediately observed and the cloudy white solution was stirred for 10 minutes at 0 °C. A solution of methyl (2S,3R)-3-hydroxy-2-[(4-(phenylcarbonyl)phenyl)carbonylamino]butanoate (**1**) (534 mg, 1.56 mmol) in MeOH (3.0 mL) was added and the reaction stirred 3 h at 0 °C, then warmed gradually to ambient temperature overnight (18 h total). Aqueous 0.5 M HCl (20 mL) was added and the solution extracted with 5:1 chloroform/isopropyl alcohol (4 × 40 mL). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give an orange foam. Purification by silica gel chromatography (increasing eluant polarity from 30:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH to 15:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) afforded 228 mg (43%) of 4-benzoyl-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino) carbonyl]propyl]benzamide.

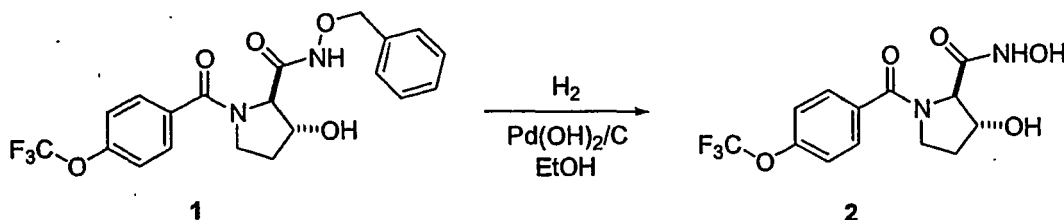
### Example 3: Synthesis of (2R,3R)-3-hydroxy-1-[(4-(trifluoromethoxy)phenyl) carbonyl] pyrrolidine-2-carboxylic acid

#### Preparation of ((2R,3R)-3-hydroxy-1-[(4-(trifluoromethoxy)phenyl)carbonyl] pyrrolidin-2-yl)-N-(phenylmethoxy)carboxamide (**2**)

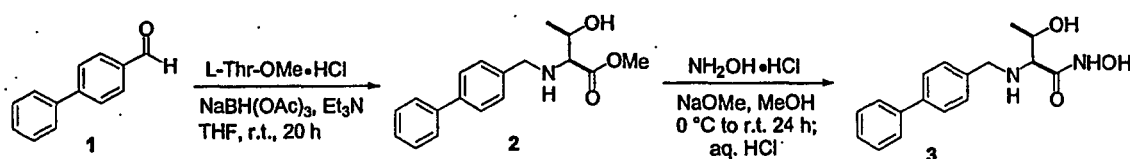
**[0141]**

**Procedure:**

**[0142]** To a solution of (2R,3R)-3-hydroxy-1-([4-(trifluoromethoxy)phenyl] carbonyl)pyrrolidine-2-carboxylic acid (1) (405 mg, 1.27 mmol), benzylhydroxylamine hydrochloride (243 mg, 1.52 mmol), HATU (556 mg, 1.46 mmol), and HOBT (178 mg, 1.32 mmol) in DMF (10 mL) at 0 °C was added diisopropylethylamine (710  $\mu$ L, 4.07 mmol) with stirring. The cooling bath was removed after one hour and the reaction mixture stirred at ambient temperature for 18 h and then diluted with EtOAc (200 mL). The organic layer was washed with 1.0 M HCl (2 x 60 mL), sat.  $\text{NaHCO}_3$  (2 x 60 mL) and  $\text{H}_2\text{O}$  (5 x 60 mL), dried over  $\text{MgSO}_4$  and concentrated to give 493 mg (92%) of ((2R,3R)-3-hydroxy-1-([4-(trifluoromethoxy)phenyl]carbonyl)pyrrolidin-2-yl)-N-(phenylmethoxy)carboxamide (2), a colorless oil that slowly crystallized upon standing. Rf (25:1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ) = 0.35.

**Preparation of (2R,3R)-3-hydroxy-1-([4-(trifluoromethoxy)phenyl] carbonyl)pyrrolidine-2-carbohydroxamic acid (2)****[0143]****Procedure:**

**[0144]** To a solution of ((2R,3R)-3-hydroxy-1-([4-(trifluoromethoxy)phenyl] carbonyl)pyrrolidin-2-yl)-N-(phenylmethoxy)carboxamide (1) (143 mg, 0.337 mmol) in EtOH (10 mL) was added 20%  $\text{Pd(OH)}_2/\text{C}$  (50 mg). The solution was purged with hydrogen gas (approx. 0.5 L from a 1 L balloon) and then stirred under an atmosphere of  $\text{H}_2$  (balloon pressure). TLC analysis showed no starting material after one hour. The solution was diluted with EtOAc (10 mL) and filtered through celite, washing with 20:1 EtOAc/EtOH (50 mL). The solution was concentrated and dried in vacuo to afford 90 mg (80%) of (2R,3R)-3-hydroxy-1-([4-(trifluoromethoxy)phenyl]carbonyl)pyrrolidine-2-carbohydroxamic acid (2) as a sticky white foam: mp 64-65 °C. Rf (10:1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ) = 0.29.

**Synthesis of N-Benzyl Threonine Analogues by Seductive Amination****Example 4: Synthesis of (2S,3R)-3-hydroxy-2-([(4-phenylphenyl)methyl]amino) butanehydroxamic acid (3).****[0145]**

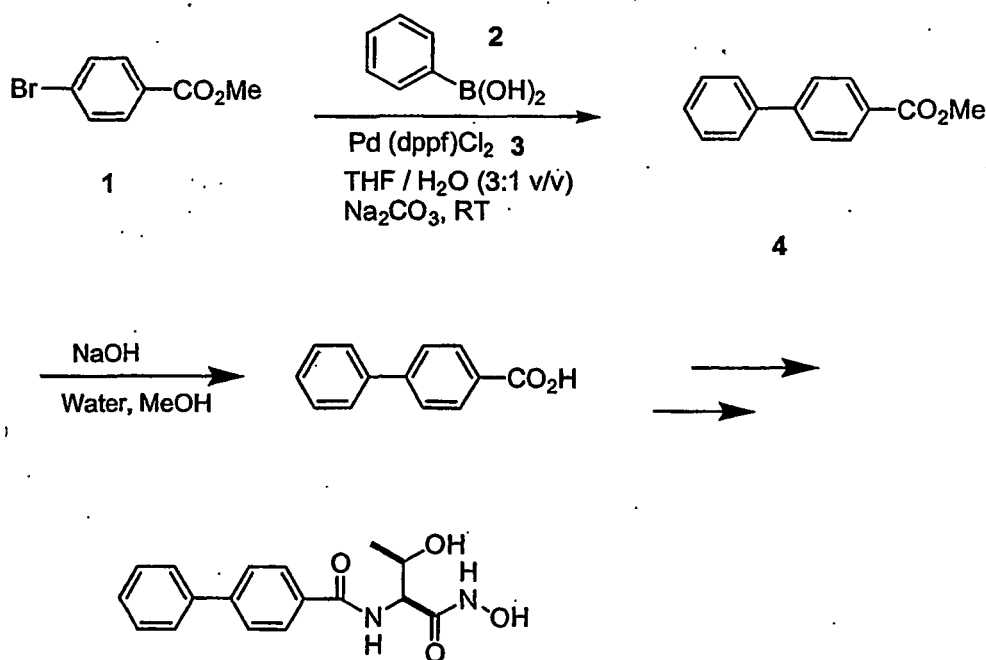


Reagent	MW	Eq.	g/ml	mmol
4-biphenylcarboxaldehyde	182.22	1.0	1.104 g	6.06
L-Thr-OMe-HCl	169.61	1.0	1.030 g	6.07
NaBH(OAc) <sub>3</sub>	211.94	1.4	1.800 g	8.49
Et <sub>3</sub> N	101.19	2.0	1.70 mL	12.1
THF			25 mL	

**[0146]** Triethylamine (1.70 mL, 12.1 mmol) was added to a stirred suspension of L-threonine methyl ester hydrochloride (1.030 g, 6.07 mmol) and 4-biphenylcarboxaldehyde (1.104 g, 6.06 mmol) in THF (25 mL). After 20 min, NaBH(OAc)<sub>3</sub> was added and the suspension stirred for 20 h. The reaction was monitored by TLC (50:1 DCM/MeOH, R<sub>f</sub>=0.4). The reaction mixture was quenched with saturated NaHCO<sub>3</sub> (50 mL), extracted with EtOAc (2 x 120 mL), dried over MgSO<sub>4</sub>, filtered and concentrated to give a yellow oil. Purification by silica gel chromatography (150:1 DCM/MeOH) afforded 1.220 g (67% yield, 98% pure) of (2S, 3R)-2-[(biphenyl-4-ylmethyl)-amino]-3-hydroxy-butyric acid methyl ester 2 as a pale yellow oil.

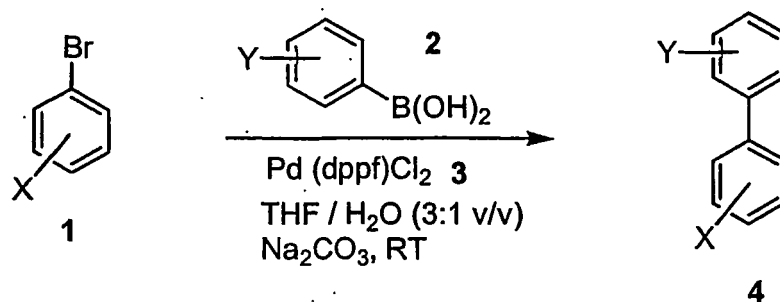
**[0147]** HPLC (260 nm, 34 min run) 14.2 min; LRMS(ES<sup>+</sup>) *m/z* 299.9 (C<sub>18</sub>H<sub>21</sub>NO<sub>3</sub> +H requires 300.10). Compound 3 was then formed by the addition of NH<sub>2</sub>OH in MeOH/NaOMe at 0°C, warming to ambient temperature of the period of several hours. LCMS MH<sup>+</sup> 301.15.

**[0148]** General Methods for Making Phenyl-benzoic acids and Phenyl-benzoate esters (see Example 5 below)



#### Suzuki Procedures Using Pd(dppf)Cl<sub>2</sub>-DCM Catalyst and a THF/H<sub>2</sub>O Mixture

**[0149]**



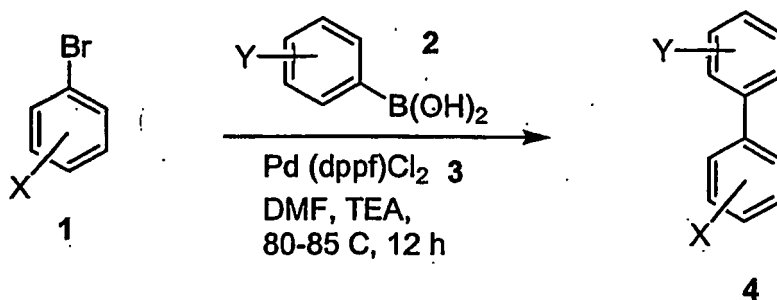
Reagent	MW	EQ	g/ml	mmol
BromoArene#1	~300	1	100 mg	~0.33
Boronic Acid #2	-	1.2	-	~0.40
Na <sub>2</sub> CO <sub>3</sub>	105.99	3	104 m	~0.99
Pd(dppf)Cl <sub>2</sub>	816.63	0.- 0.2	27-54 mg	~0.033-0.066
THE (3) (sparged with argon for 5 min.)			0.75 ml	
water(1) (sparged with argon for 5 min.)			0.25 ml	

### Standard Procedure

[0150] 1 eq aryl halide (1) was added to 1.2 eq. (2) and Pd(dppf)Cl<sub>2</sub> in THF, followed by addition of water and stirred 8 hours at RT. Upon completion (usually over night), the reactions are diluted with ethyl acetate (5-10 ml) and water (1ml). The organic layer is separated and washed with Na<sub>2</sub>CO<sub>3</sub> (2x3 ml), water (1x3 ml), brine (1x3 ml), dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in an 8 ml glass vial. The residue is dissolved in DMSO and injected on a preparatory HPLC reverse phase column to afford >80 % yield.

### Suzuki Procedures Using Pd(dppf)Cl<sub>2</sub>-DCM Catalyst and DMF Solvent

[0151]



Reagent	MW	EQ	g/ml	mmol
BromoArene #1	~500	1	20 mg	~0.04
Boronic Acid #2	~200	2	~14 mg	~0.08
Pd(dppf)Cl <sub>2</sub>	816.63	0.25	10 mg	~0.01-0.02
TEA	101.19	5	28 $\mu$ L	~0.2
DMF (dry & sparged with argon for 5 min.)			0.5 ml	

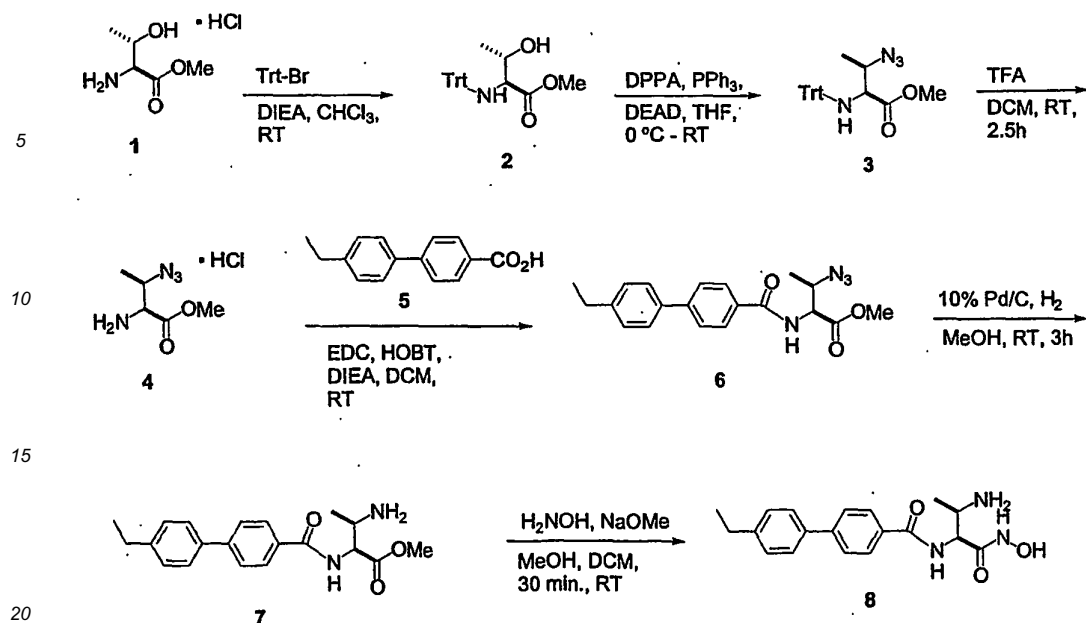
### Standard Procedure

[0152] The haloarene 1 and boronic acid 2 were weighed out and placed in the reaction flask. The DMF was sparged with argon for 5-10 minutes, followed by TEA addition, and the reaction was lightly bubbled with argon. The solid Pd(dppf)Cl<sub>2</sub> catalyst was added in one portion. The vial was flushed with argon, capped tight and stirred or shaken at ~80 °C. Upon reaching completion (over night), the reaction was filtered and injected on a preparatory HPLC reverse phase column (80% yield).

### Synthesis of Methyl DAP Analogues

Example 5: 3-(R)-Amino-2-(S)-[(4'-ethyl-biphenyl-4-carbonyl)-amino]-butyl-hydroxamic acid (8)

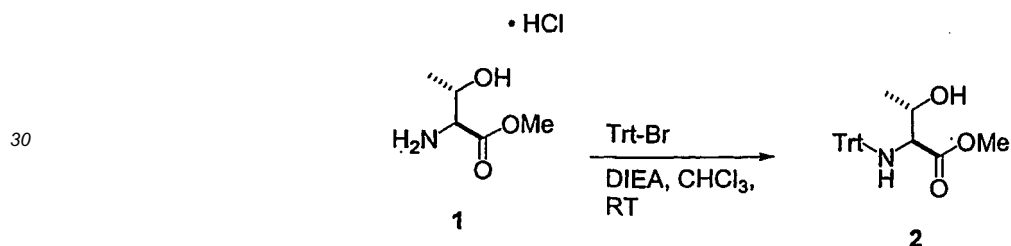
[0153]



# Preparation of N-triphenylmethyl allo-threonine methyl ester (2).

[0154]

25



Reagent	MW	EQ	g/ml	mmol
H-allo-Thr-OMeHCl (1)	169.7	1.2	2.0 g	12.0
Trt-Br	323.24	1.0	3.23 g	10.0
DIEA	129.25	3.0	5.2 ml	30.0
CHCl <sub>3</sub> (dry)			100ml	

[0155] For similar-procedures see: Righi, P.; Scardovi, N.; Marotta, E.; ten Holte, P.; Zwanenburg, B. Organic Letters 2002, 4(4), 497-500.

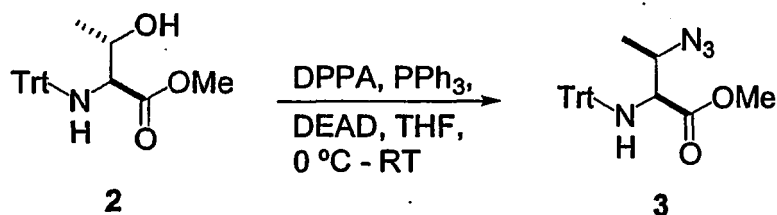
45 [0156] A solution of trityl bromide (3.2g, 10.0mmol) in CHCl<sub>3</sub> (40ml) was added dropwise to a stirred solution of allo-threonine methyl ester HCl salt (1) (2.0g, 12.0mmol) and DIEA (5.2ml, 30.0mmol) in CHCl<sub>3</sub> (60ml) at rt under N<sub>2</sub>. The reaction could be followed by TLC eluting with EtOAc/Hex (40:60) (R<sub>f</sub>=0.3). After stirring 12 h, the reaction was concentrated to a brown oil. The crude product was diluted with EtOAc (170ml) and washed with 0.2 N citric acid (2x50ml), water (2x50ml), brine (50ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to yield 3.73g (85% yield, 95% pure) of a yellow solid.

50 [0157] HPLC(220nm, 41min. run) 30.90 min.; HPLC(220nm, 17min. run) 14.86 min.; LCMS: LC(214nm) 3.06 min., MS(ES+) m/z 376.2 (C<sub>24</sub>H<sub>25</sub>NO<sub>3</sub> +H requires 376.18).

# Preparation of 3-(R)-Azido-2-(S)-(trityl-amino)-butyric acid methyl ester (3).

55

[0158]



Reagent	MW	Eq.	g/ml	mmol
Trt-allyl-Thr-OMe (2)	375.46	1.0	4.68 g	10.88
PPh <sub>3</sub>	262.29	1.0	2.85 g	10.88
DEAD (neat)	174.16	1.6	2.93 ml	17.82
DPPA	275.7	2.7	6.40 ml	29.7
THF (dry)			50 ml	

**[0159]** For similar procedures see: Matsuda, A.; Yasuoka, J.; Sasaki, T.; Ueda, T. J. Med. Chem. 1991, 34, 999-1002.

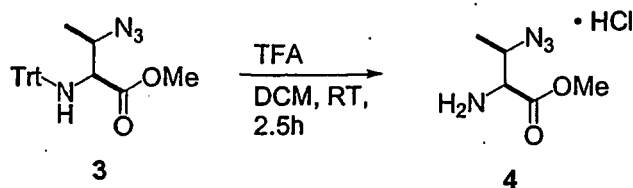
**[0160]** A solution of pure DEAD (2.9ml, 17.8mmol) in THF (5ml) was added slowly dropwise to a stirred solution of trt-allyl-threonine methyl ester (2) (4.1g, 10.9mmol) and PPh<sub>3</sub> (2.9g, 10.9mmol) in THF (40ml) at 0 °C under N<sub>2</sub>. After 3 min., a solution of DPPA (6.4ml, 29.7mmol) in THF (5ml) was added to the orange-yellow reaction solution at 0 °C. After 1 h, the reaction was allowed to warm to rt. After 40h, the reaction had reached completion by TLC (Hexane/DCNVEtOAc (64:20:16) (R<sub>f</sub>-0.6)) and LCMS. The yellow solution was concentrated to give 18g of crude material that was purified by column chromatography eluting with Hexane/EtOAc (88:12) giving 3.5g of 70% pure product after evaporation. The product was purified again (to remove trityl alcohol and a crotyl side-product formed during the reaction by elimination) by column chromatography eluting with Hexane/DCM/EtOAc (76:20:4) giving 1.65g (38% yield) of a pale yellow oil after concentration and drying in vacuo. Note that the trityl protecting group would hydrolyze when exposed to TFA while running the sample on HPLC.

**[0161]** Alternately, the reaction could be carried out in dry DCM. A reaction using 5.44g (14.5 mmol) of trt-allyl-threonine methyl ester (2) in DCM (100ml) with PPh<sub>3</sub> (3.8g, 14.5mmol), pure DEAD (3.4ml, 21.8mmol) in DCM (5ml) and DPPA (6.3ml, 24.0mmol) in DCM (10ml) were combined following the procedure above. After 3 days, the reaction did not progress further by TLC and LCMS. After the same work up, 2.97g of the product was obtained in 51% yield.

**[0162]** HPLC(220nm, 41min. run) 40.5 min.; BPLC(220nm, 17min. run) 16.32 min.; LCMS: LC(214nm) 3.7 min., MS (ES+) m/z 401.2 (C<sub>24</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub> +H requires 401.15).

#### Preparation of 2-(S)-Amino-3-(R)-azido-butyric acid methyl ester HCl Salt (4).

**[0163]**



Reagent	MW	EQ	g/ml	mmol
Trt-Azido-Thr-OMe (3)	400.47	1.0	4.79 g	11.98
TFA			57 ml	
CHCl <sub>3</sub> (dry)			3 ml	

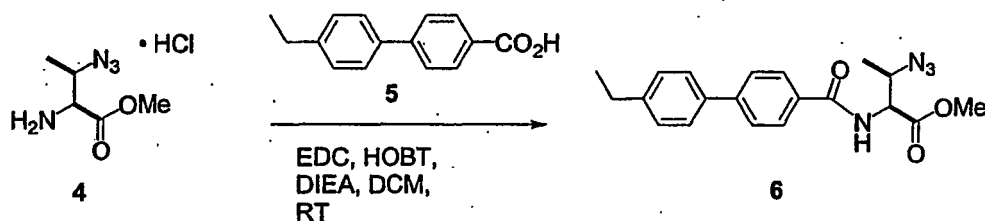
**[0164]** A solution of Trt-Azido-Thr-OMe (3) (4.8g, 12.0mmol) was dissolved in a 95% TFA/DCM solution (60ml) at rt with stirring. After 2.5 h, the reaction was complete by LCMS. The bright yellow solution was diluted with 0.5 N aq. HCl

(300ml). The aqueous layer was extracted with DCM (2x30ml) and then lyophilized to dryness. The white solid was dissolved in AcCN/water (50:50) (100ml) and again lyophilized to dryness to produce a consistent powder and remove as much of the TFA as possible. The azido-Thr product (4), 2.26g (97% yield, 95% pure) of a white solid, was obtained as the HCl salt.

[0165] HPLC(220nm, 41min. run) 7.91 min.; HPLC(220nm, 17min.run) 3.36 min; LCMS: LC(214nm) 0.48 min., MS (ES+) m/z 159.3 ( $C_5H_{10}N_4O_2 + H$  requires 159.08).

**Preparation of 3-(R)-Azido-2-(S)-[(4'-ethyl-biphenyl-4-carbonyl)-amino]-butyric acid methyl ester (6).**

[0166]



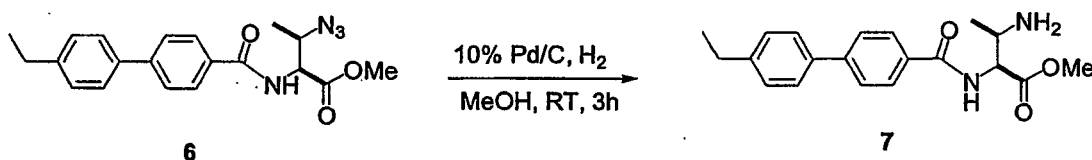
Reagent	MW	EQ	g/ml	mmol
Azido-Thr-OMe-HCl (4)	194.62	1.0	195 mg	1.0
Biphenyl Acid (5)	226.27	1.0	226 mg	1.0
HOBT	153	1.0	158 mg	1.0
EDC-HCl	191.17	1.3	249 mg	1.3
DIEA	129.25	2.5	0.44 ml	2.5
DCM (dry)			10 ml	

[0167] A EDC·HCl (249mg, 1.3mmol) was added to a stirred colorless solution of azido-Thr-OMe-HCl (4) (195mg, 1.0mmol), HOBT (158mg, 1.0mmol), 4'-Ethyl-biphenyl-4-carboxylic acid (5) (226mg, 1.0mmol) and DIEA (0.44ml, 2.5mmol) in DCM (10ml) at rt under  $N_2$ . After 24 h, the reaction had reached completion by TLC (Hexane/EtOAc (60:40) (Rf.3)) and LCMS. The reaction was evaporated under reduced pressure to a brown tar. The crude product was dissolved in EtOAc (100ml) and washed with 0.2N aq. HCl (2x50ml), aq. sat.  $NaHCO_3$  (50ml), brine (50ml), dried ( $Na_2SO_4$ ), filtered and concentrated under reduced pressure to yield a crude brown solid. The crude material was further purified by column chromatography eluting with Hexane/EtOAc (70:30) giving 245mg (67% yield) of pure product after evaporation and drying in vacuo.

[0168] HPLC(220nm, 41min. run) 33.87 min.; HPLC(220nm, 17min. run) 15.61 min; LCMS: LC(214nm) 3.25min., MS (ES+) m/z 367.2( $C_{20}H_{22}N_4O_3 + H$  requires 367.17).

**Preparation of 3-(R)-Amino-2-(S)-[(4'-ethyl-biphenyl-4-carbonyl)-amino]-butyric acid methyl ester (7).**

[0169]



Reagent	MW	EQ	g/ml	mmol
Biphenyl Azido-Thr (6)	366.41	1.0	244 mg	0.67

(continued)

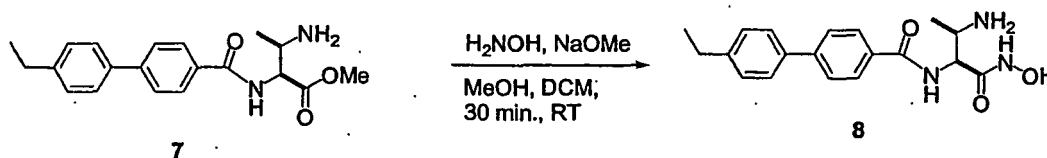
Reagent	MW	EQ	g/ml	mmol
10% Pd/C			200 mg	
H <sub>2</sub> (gas)			12" balloon	
MeOH (dry)			10 ml	

**[0170]** A solution of biphenyl azido-Thr methyl ester (6) (244mg, 0.67mmol) in MeOH (10ml) was made by sonicating until the milky precipitate cleared. After bubbling nitrogen through the reaction solution for 30 sec., 10% Pd/C was added in one portion. The reaction was stirred under nitrogen at RT. The reaction was exposed to aspirator vacuum to remove the nitrogen and then opened to the hydrogen gas at balloon pressure (~1 atm). The reaction stirred for 3h at which time the hydrogen was exchanged for nitrogen. The reaction was filtered through a pad of celite to remove the palladium. The celite pad was washed with MeOH (30ml). The combined fractions of MeOH were evaporated under reduced pressure and dried in vacuo to give 225mg (99% yield) of pure produce (7) as a white solid.

**[0171]** HPLC(220nm, 17min. run) 10.79 min.; LCMS: LC(214nm) 2.21 min., MS(ES+) m/z 341.2 (C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub> +H requires 341.18).

### Preparation of 3-(R)-Amino-2-(S)-[(4'-ethyl-biphenyl-4-carbonyl)-amino]-butyl-hydroxamic acid (8)

**[0172]**



Reagent	MW	EQ	g/ml	mmol
Amino-Thr-OMe (7)	340.42	1.0	225 mg	0.66
H <sub>2</sub> NOH·HCl	69.49	10.0	460 mg	6.6
NaOMe	54.02	~12.0	~430 mg	7.92
MeOH (dry)			7 ml	
DCM (dry)			5 ml	

**[0173]** To a stirred suspension of biphenyl-amino-Thr methyl ester (7) (225mg, 0.6mmol) and hydroxylamine HCl salt (460mg, 6.6mmol) in MeOH (7ml) and DCM (5ml) was added fresh solid NaOMe powder (430mg, 7.92mmol) in one portion. After stirring for 2 min. at rt under nitrogen, the pH of the reaction on wet pH paper was approximately 7-8. The suspension had change from larger particles of white solid to a finely-divided milky consistency. The pH of the reaction was checked after adding small portions of NaOMe (50-100mg) and allowing 2 min. for the reaction to equilibrate. The pH of the reaction reached a stable 11-12 after the final portion of NaOMe was added (250mg total). The reaction was initiated at pH 11 and proceeded quickly. After 30 min., the reaction reached 85% completion as determined by LCMS, and the reaction was placed in a -10 °C bath. The cold mixture filtered over fine filter paper on a Büchner funnel. The white residue was washed with MeOH (15ml). The organic fractions were collected and concentrated under reduced pressure to give crude product (750mg). The crude product (only one 150 mg portion) was dissolved in DMSO (1ml), AcCN (100μl) and water (100μl), passed through a Teflon syringe filter, and the clear filtrate was injected on a preparative HPLC. The purification used a 20x50 mm Ultro 120 C18 column running a 22 ml/min 2% gradient (AcCN/water, 0.1 % TFA) for 16 min. The purified fractions were lyophilized to dryness. The product as the TFA salt was dissolved in AcCN/ water (50:50) (5ml), 1N aq. HCl (1 equivalent) and lyophilized again to give 11.5 mg of white powder as an HCl salt (23% yield).

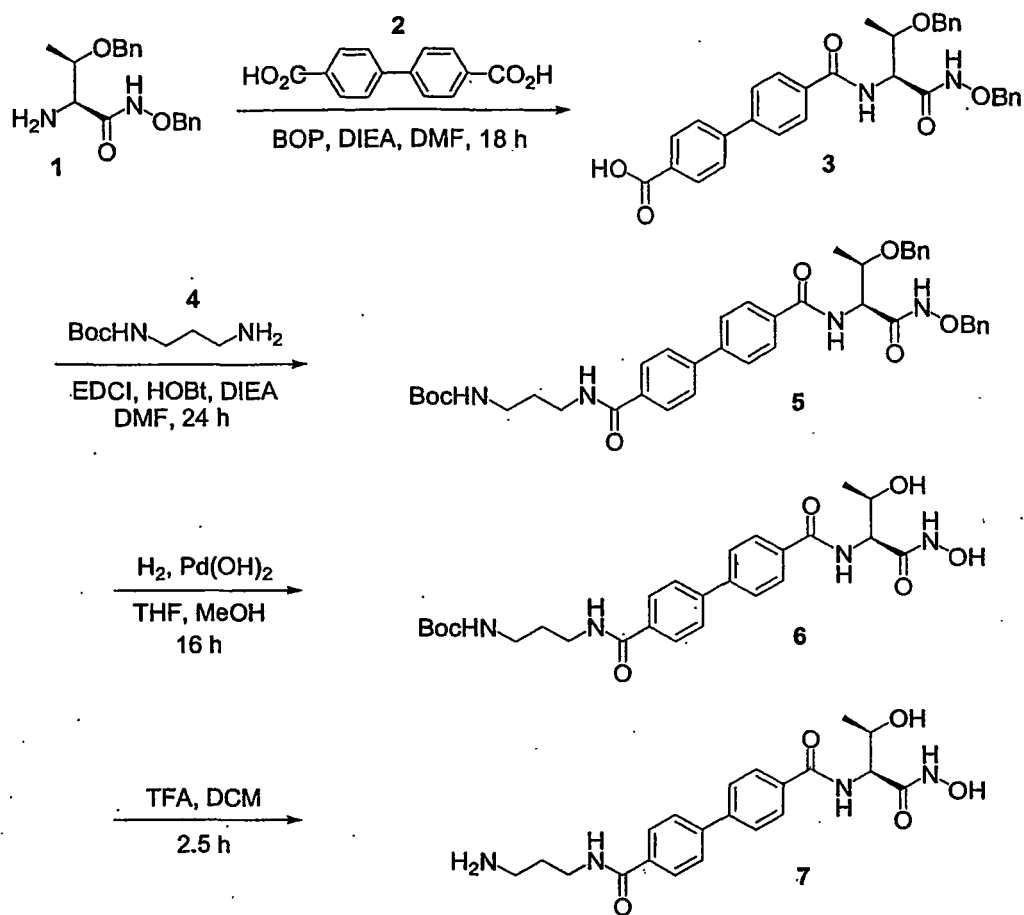
**[0174]** HPLC(220nm, 41min. run) 19.31 min.; HPLC(220nm, 17min. run) 9.39 min; LCMS: LC(214nm) 1.98 min., MS (ES+) m/z 342.2 (C<sub>19</sub>H<sub>23</sub>N<sub>3</sub>O<sub>3</sub> +H requires 342.17).

## Synthesis of 4'-Benzamide Biphenyl Threonine Hydroxamic Acid

**Example 6: Biphenyl-4,4'-dicarboxylic acid 4'-[(3-Boc-amino-propyl)-amide] 4-(((2R)-hydroxy-(1S)-hydroxycarbamoyl-propyl)-amide] (6), and**

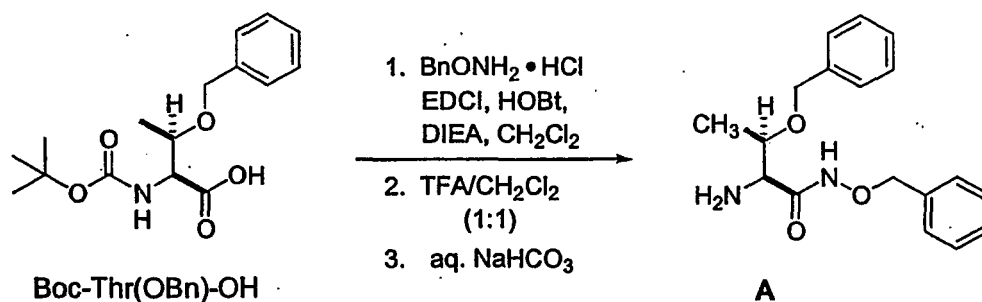
**Example 7: Biphenyl-4,4'-dicarboxylic acid 4'-[(3-amino-propyl)-amide] 4-(((2R)-hydroxy-(1S)-hydroxycarbamoyl-propyl)-amide] (7)**

[0175]



## Synthesis of (2S,3R)-2-amino-3-(phenylmethoxy)-N-(phenylmethoxy)butanamide (1)

[0176]



**Procedure:**

**[0177]** To a suspension of benzylhydroxylamine hydrochloride (8.310 g, 52.06 mmol), Boc-Thr(OBn)-OH (14.01 g, 45.28 mmol), EDCI (10.01 g, 52.21 mmol), and HOBt (6.90 g, 51.06 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (300 mL) at 0 °C was added diisopropylethylamine (28.3 mL, 162 mmol) with stirring. The cooling bath was removed after one hour and the reaction mixture stirred at ambient temperature for 20 h and was then diluted with CH<sub>2</sub>Cl<sub>2</sub> (300 mL). The organic layer was washed with 1.0 M HCl (2 x 200 mL), sat. NaHCO<sub>3</sub> (2 x 200 mL) and brine (200 mL), dried over MgSO<sub>4</sub> and concentrated to give 14.5 g of a white solid. The crude solid was treated with a solution of trifluoroacetic acid (90 mL) in CH<sub>2</sub>Cl<sub>2</sub> (90 mL) and stirred for 2.5 h. The reaction mixture was concentrated by rotary evaporation and then diluted with CH<sub>2</sub>Cl<sub>2</sub> (600 mL). The organic layer was washed with sat. NaHCO<sub>3</sub> (2 x 200 mL), dried over MgSO<sub>4</sub> and concentrated to give a dark orange oil. Purification by silica gel chromatography (50:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) afforded (2S,3R)-2-amino-3-(phenyl-methoxy)-N-(phenylmethoxy) butanamide (A) (8.9 g,) as a pale yellow oil. R<sub>f</sub> (50:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH on silica gel) = 0.2.

**Preparation of (1S,2R)-4'-(2-benzyloxy-1-benzyloxycarbamoyl-propylcarbamoyl)-biphenyl-4-carboxylic acid (3).**

**[0178]**

Reagent	MW	Eq.	g/mL	mmol
Amine (1)	314.38	1.0	0.944 g	3.00
Dicarboxylic acid (2)	242.23	1.9	1.360 g	5.61
BOP	442.3	1.5	2.007 g	4.54
DIEA	129.25	3.3	1.7 mL	9.76
DMF			200 mL	

**[0179]** To a suspension of 4,4'-biphenyldicarboxylic acid **2** (1.360 g, 5.61 mmol) in DMF (180 mL) was added BOP (2.007 g, 4.54 mmol) and DIEA (1.7 mL, 9.8 mmol). A solution of (1S,2R)-2-amino-3,N-bis-benzyloxy-butyramide **1** (944 mg, 3.00 mmol) in DMF (20 mL) was added and the reaction stirred for 18 h. The solution was diluted with EtOAc (250 mL) and washed with 1.0 M HCl (500 mL). The aqueous layer was extracted with EtOAc (250 mL) and the organic layers combined. The organic layer was washed with 1.0 M HCl (250 mL), dried over MgSO<sub>4</sub>, and concentrated to give a crude yellow solid. Purification by silica gel chromatography (60:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) gave 210 mg (1S,2R)-4'-(2-benzyloxy-1-benzyloxycarbamoyl-propylcarbamoyl)-biphenyl-4-carboxylic acid **3**. (13% yield) as a yellow solid. R<sub>f</sub> = 0.80 (10:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH); LRMS (ES+) m/z 539.1 (C<sub>32</sub>H<sub>30</sub>N<sub>2</sub>O<sub>6</sub> + H requires 539.22).

**Preparation of biphenyl-4,4'-dicarboxylic acid 4'-[(3-(Boc)-amino-propyl)-amide]-4-[(2R)-benzyloxy-(1S)-benzyloxycarbamoyl-propyl)-amide] (5).**

**[0180]**

Reagent	MW	Eq.	g/mL	mmol
Biphenylcarboxylic acid (3)	538.59	1.0	0.200 g	0.371
Amine (4)	174.24	1.1	0.071 g	0.407
EDCI	191.71	1.1	0.078 g	0.407
HOBt	135.13	1.0	0.052 g	0.385
DIEA	129.25	2.7	180 μL	1.0
DMF			2 mL	

**[0181]** To a solution of biphenylcarboxylic acid **3** (200 mg, 0.371 mmol), EDCI (78 mg, 0.407 mmol), and HOBt (52 mg, 0.385 mmol) in DMF (2 mL) was added t-Butyl N-(3-aminopropyl)carbamate **4** (71 mg, 0.407 mmol) and DIEA (180 μL, 1.0 mmol). The reaction mixture was stirred 24 h, diluted with EtOAc (150 mL), washed with 1.0 M HCl (2 x 60 mL), saturated NaHCO<sub>3</sub> (2 x 60 mL), H<sub>2</sub>O (3 x 60 mL), dried over MgSO<sub>4</sub> and concentrated to give a crude white solid. Purification by silica gel chromatography (25:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) afforded 194 mg (75% yield) of biphenyl-4,4'-dicarboxylic acid 4'-[(3-(Boc)-amino-propyl)-amide]-4-[(2R)-benzyloxy-(1S)-benzyloxycarbamoyl-propyl)-amide] **5** as a white solid. R<sub>f</sub> = 0.15 (50:1 CH<sub>2</sub>Cl/MeOH); LRMS (ES+) m/z 695.2 (C<sub>40</sub>H<sub>46</sub>N<sub>4</sub>O<sub>7</sub> + H requires 695.35).



**Preparation of Biphenyl-4,4'-dicarboxylic acid 4'-[(3-Boc-amino-propyl)-amide] 4-(((2R)-hydroxy-(1S)-hydroxycarbamoyl-propyl)-amide] (6).**

**[0182]**

Reagent	MW	Eq.	g/mL	mmol
Biphenyl diamide (5)	694.82	1.00	0.190 g	0.273
Pd(OH) <sub>2</sub> (20%/C)	106.42	0.15	0.020 g	0.040
H <sub>2</sub> (g)			balloon	
THF			5.0 mL	
MeOH			3.0 mL	

**[0183]** A solution of dibenzyl-protected threonine hydroxamic acid 5 (190 mg, 0.273 mmol) in THF (5 mL) and MeOH (3 mL) was charged with Pd(OH)<sub>2</sub> (20%/C, 20 mg, 0.04 mmol) and stirred under a hydrogen atmosphere (balloon pressure) for 16 h. The crude mixture was filtered through a plug of celite eluting with 2:1 MeOH/THF (15 mL) and concentrated to give an orange syrup. Purification by silica gel chromatography (5:1:1 THF/MeOH/CH<sub>2</sub>Cl<sub>2</sub>) afforded 110 mg (78% yield) of biphenyl-4,4'-dicarboxylic acid 4'-[(3-Boc-amino-propyl)-amide] 4-(((2R)-hydroxy-(1S)-hydroxycarbamoyl-propyl)-amide] as a white foam, mp 75-77 °C. R<sub>f</sub> = 0.20 (10:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH); LRMS (ES+) m/z 515.4 (C<sub>26</sub>H<sub>34</sub>N<sub>4</sub>O<sub>7</sub> + H requires 515.26).

**Preparation of Biphenyl-4,4'-dicarboxylic acid 4'-[(3-amino-propyl)-amide] 4-(((2R)-hydroxy-(1S)-hydroxycarbamoyl-propyl)-amide] (7).**

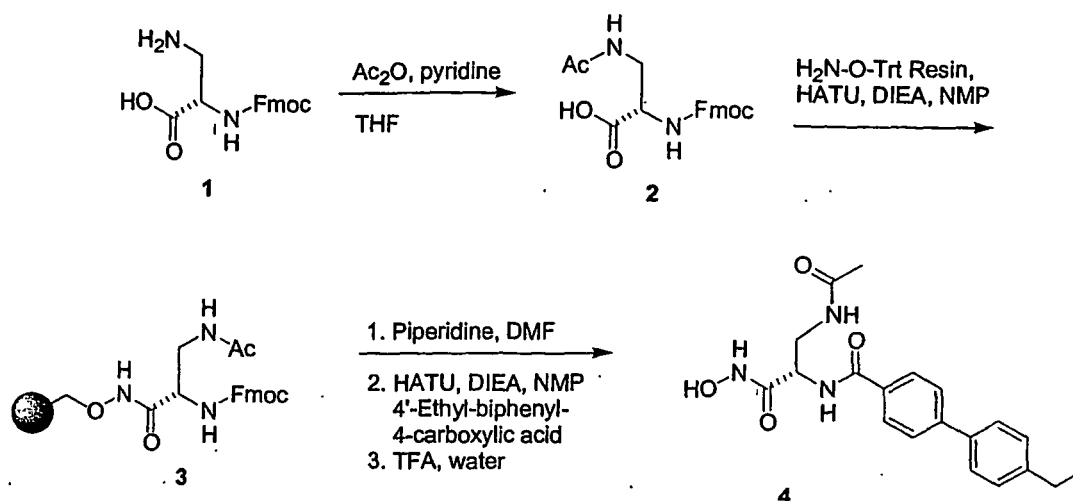
**[0184]**

Reagent	MW	Eq.	g/mL	mmol
Boc-protected amine (6)	514.57	1.00	0.080 g	0.155
TFA			3.0 mL	
CH <sub>2</sub> Cl <sub>2</sub>			3.0 mL	

**[0185]** A flask containing Boc-protected amine 6 (80 mg, 0.155 mmol) was treated with 50% TFA/CH<sub>2</sub>Cl<sub>2</sub> (6.0 mL) and stirred for 2.5 h. The reaction mixture was concentrated by rotary evaporation to give a brown syrup. Purification by RP-HPLC (C<sub>18</sub> column, CH<sub>3</sub>CN gradient 5-70%, 0.1% TFA, UV analysis 300 nm, 36 min) and lyophilization of the collected fractions afforded 14 mg (21% yield) of biphenyl-4,4'-dicarboxylic acid 4'-[(3-amino-propyl)-amide] 4-(((2R)-hydroxy-(1S)-hydroxycarbamoyl-propyl)-amide] as a white solid. LRMS (ES+) m/z 415.3 (C<sub>21</sub>H<sub>26</sub>N<sub>4</sub>O<sub>5</sub> + H requires 415.20); RP-HPLC (300 nm, 36 min run) 18.2 min.

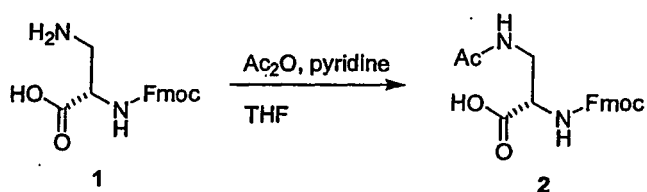
**Example 8: Synthesis of N-(2-(N-hydroxycarbamoyl)(2S)-2-[4-(4-ethylphenyl)phenyl]carbonylamino)ethyl) acetamide (4)**

**[0186]**



Preparation of 3-Acetylamino-2-(9H-fluoren-9-ylmethoxycarbonylamino)-propionic acid (2).

[0187]

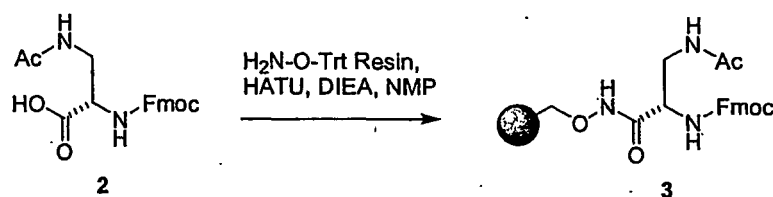


Reagent	MW	EQ	g/ml	mmol
Fmoc-DAP-H (1)	326.4	1.0	980 mg	3.0
Acetic anhydride	102.09	1.5	425 $\mu$ L	4.5
Pyridine	79.1	2.0	483 $\mu$ L	6.0
THF			20 ml	

[0188] Acetic anhydride in THF (5ml) was added to a cloudy mixture of Fmoc-DAP-H (1) (980mg, 3.0mmol) and pyridine (483 $\mu$ L, 6.0mmol) in THF (15ml) with stirring at rt. After 4 hours, the clear pale yellow solution had reacted completely by LCMS. The reaction was evaporated under reduced pressure. The residue was dissolved in EtOAc (150ml) and washed with 0.1M NaHSO<sub>4</sub> (50ml), water (50ml), sat. brine (50ml), dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give 1.1 g of crude product as a white solid. The crude product was purified by prep. HPLC to give 0.99 g (90% yield) of acyl-DAP (2).

Preparation of (2-Acetylamino-1-hydroxycarbamoyl-ethyl)-carbamic acid 9H-fluoren-9-ylmethyl ester trityl resin in (3).

[0189]

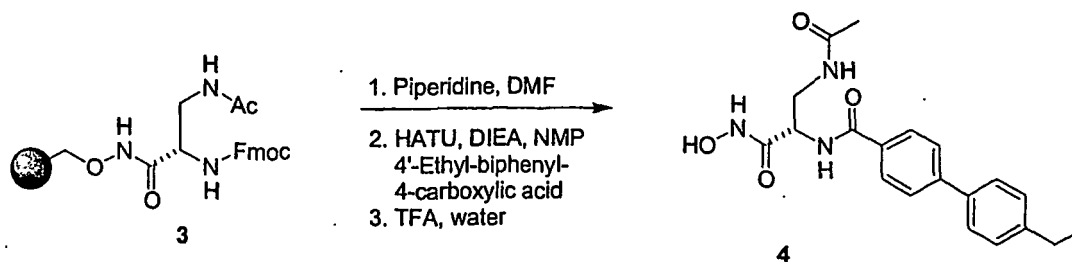


Reagent	MW	EQ	g/ml	mmol
H <sub>2</sub> N-O-Trt Resin		1.0	120 mg	0.113
Fmoc-DAP(Ac)-H (1)	368.4	5.0	980 mg	0.564
HATU	380	5.0	0.146 g	0.564
DIEA	129.25	10.0	196 $\mu$ l	1.13
NMP			1.7 ml	

**[0190]** A solution of Fmoc-DAP(Ac)-H (1) (980mg, 0.56mmol), HATU (0.146g, 0.56mmol) in NMP (1.7ml) was made. After 2 min. of shaking, the activated acid was added to the deprotected H<sub>2</sub>N-O-Trt Resin (120 mg, 0.113mmol) at rt with shaking. [Deprotection of the Fmoc group from the resin was accomplished using 20% piperizine in DMF (4ml) for 2 hours twice. The resin was drained and washed with DMF (2x5ml) and DCM (2x5ml).] After shaking for 20 hours, the reaction was drained and washed with DMF (2x5ml) and DCM (2x5ml). The resin was dried and used as is in the next reaction.

**Preparation of N-(2-(N-hydroxycarbamoyl)(2S)-2-([4-(4-ethylphenyl)phenyl] carbonylamino)ethyl)acetamide (4)**

**[0191]** Preparation of (2-Acetyl-amino-1-hydroxycarbamoyl-ethyl)-carbamic acid 9H-fluoren-9-ylmethyl ester trityl resin (3).

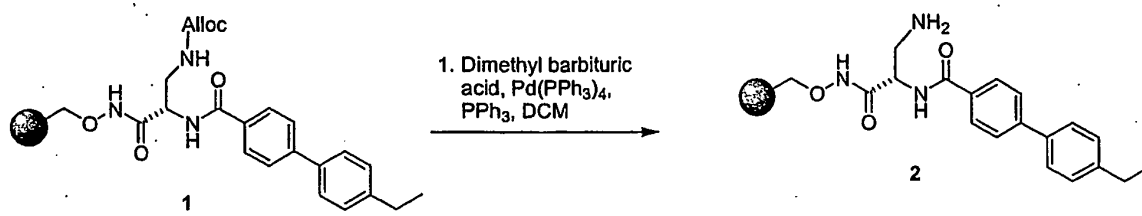


Reagent	MW	EQ	g/ml	mmol
Fmoc-DAP(Ac)-Trt Resin (3)		1.0	120 mg	0.113
4'-Etbiphenyl 4-carboxy acid	226.3	5.0	91 mg	0.4
HATU	380	5.0	152 mg	0.4
DIEA	129.25	10.0	140 $\mu$ l	0.8
NMP			1.0 ml	

**[0192]** The resin was treated with 20% piperizine in DMF (4ml) for 2 hours twice. The resin was drained and washed with DMF (2x5ml) and DCM (2x5ml). The resin was dried *in vacuo*. A solution of 4'-Ethyl-biphenyl-4-carboxylic acid (91mg, 0.4mmol), HATU (152g, 0.4mmol) in NMP (1.0ml) was made. After 2 min. of shaking, the activated acid was added to the deprotected H-DAP(Ac)-Trt resin (120 mg, 0.113mmol) at rt with shaking. After shaking for 18 hours, the reaction was drained and washed with DMF (2x5ml) and DCM (2x5ml) The resin was dried *in vacuo*. The product was cleaved from the resin through treatment with a solution of TFA (500 $\mu$ L), DCM (500 $\mu$ L) and water (50 $\mu$ L) for 25 min. The resin was filtered and washed with fresh DCM (2ml). The combined TFA and DCM fractions are evaporated under reduced pressure. The residue was diluted with CH<sub>3</sub>CN/water (1:1) (10ml) and lyophilized. The crude product was purified by prep. HPLC. The crude product was dissolved in DMSO (1ml), passed through a Teflon syringe filter, and the clear filtrate was injected on a preparative HPLC. The purification used a 20x50 mm Ultra 120 C18 column running a 22 ml/min 2% gradient (AcCN/water, 0.1% TFA) for 16 min. The purified fractions were lyophilized to dryness. The solid residue was lyophilized again from CH<sub>3</sub>CN/water (1:1) (5ml) give 8.6 mg of pure product (4) (~21% yield).

**Example 9: Synthesis of 4'-Ethyl-biphenyl-4-carboxylic acid (1-hydroxycarbamoyl-2-methanesulfonylamino-ethyl)-amide (3)****Preparation of 4'-Ethyl-biphenyl-4-carboxylic acid (2-amino-1-hydroxycarbamoyl-ethyl)-amide, trityl resin (2).**

[0193]

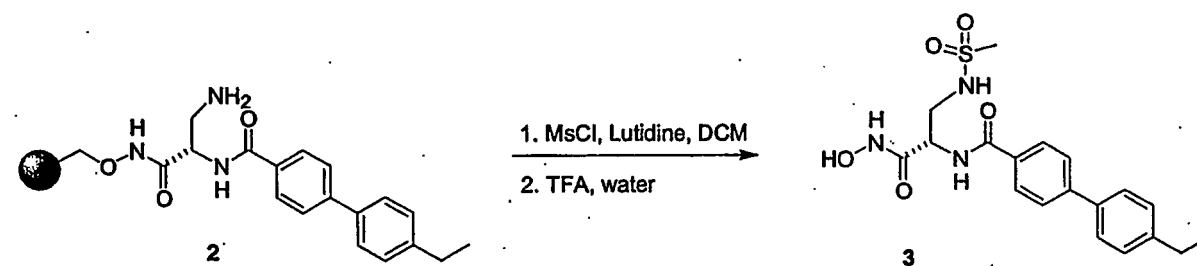


Reagent	MW	EQ	g/ml	mmol
Biphenyl-DAP(Alloc)-Trt Resin (1)		1.0	500 mg	0.35
Dimethyl barbituric acid	156.14	10.0	600 mg	3.5
Pd(PPh <sub>3</sub> ) <sub>4</sub>	1135.6	1.0	438 mg	0.35
PPh <sub>3</sub>	262.3	2.0	202 mg	0.7
DCM			11.0 ml	

[0194] Pd(PPh<sub>3</sub>)<sub>4</sub> (438mg, 0.35mmol) was added to a vial containing biphenyl-DAP(Alloc)-Trt Resin (1) (500mg, 0.35mmol), Dimethyl barbituric acid (600mg, 3.5mmol) and PPh<sub>3</sub> (438mg, 0.35mmol) in DCM (11ml) at rt under argon. The mixture was sparged with argon and shaken for 16 hours. The bright yellow mixture was drained and washed with DMF (8x10ml) and DCM (8x10ml). The resin was dried *in vacuo* to give the deprotected DAP resin 2.

**Preparation of 4'-Ethyl-biphenyl-4-carboxylic acid (1-hydroxycarbamoyl-2-methane sulfonylamino-ethyl)-amide (3).**

[0195]



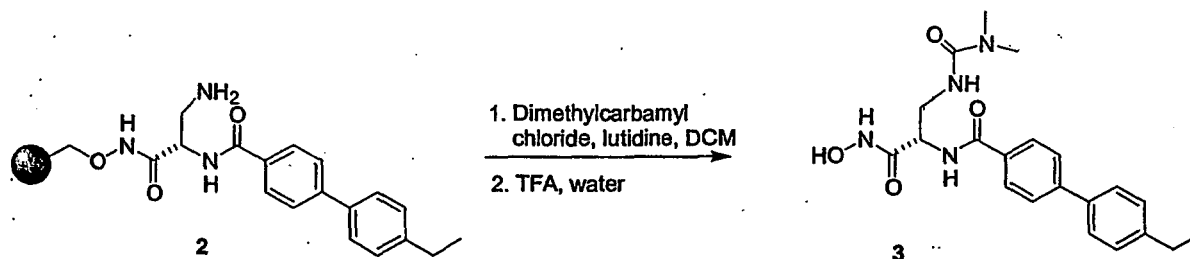
Reagent	MW	EQ	g/ml	mmol
Biphenyl-DAP-Trt Resin (2)		1.0	160 mg	0.11
Methanesulfonyl chloride	114.55	10.0	85 $\mu$ L	1.1
Lutidine	107.16	15.0	190 $\mu$ L	1.6
DCM			1.5 ml	

[0196] Methanesulfonyl chloride (85 $\mu$ L, 1.1mmol) was added to a mixture of deprotected DAP resin (2) (160mg, 0.11mmol) and lutidine (190 $\mu$ L, 1.6mmol) in DCM (1.5ml). After shaking for 16 hours, the mixture was drained and washed with DMF (10x2ml) and DCM (5x2ml). The product was cleaved from the resin through treatment with TFA/

water (4:1) (1.5ml). After shaking for 45 min., the TFA solution was collected from the resin by filtration, and the resin was washed with TFA (1ml) and TFA/water (1:1) (10ml). The combined TFA fractions were concentrated under reduced pressure to a reddish-brown solid. The product, identified by LCMS, was purified by prep. HPLC using a 20x50 mm Ultro. 120 C18 column running a 22 ml/min 4% gradient (AcCN/water, 0.1% TFA) for 16 min. The purified fractions were lyophilized to dryness. The solid residue was lyophilized again from CH<sub>3</sub>CN/water (1:1) (5ml) give 4 mg of pure product as a white solid (**3**) (~9% yield).

**Example 10: Synthesis of 4'-Ethyl-biphenyl-4-carboxylic acid [2-(3,3-dimethyl-ureido)-1-hydroxycarbamoyl-ethyl]-amide (**3**) (Continued from compound **2** of Example 9 above)**

[0197]

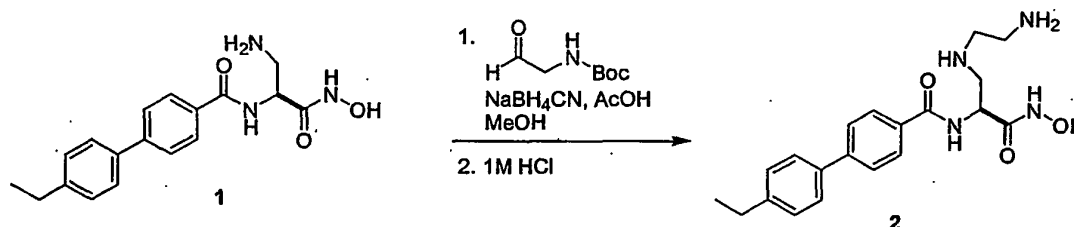


Reagent	MW	EQ	g/ml	mmol
Biphenyl-DAP-Trt Resin ( <b>2</b> )		1.0	125 mg	0.096
Dimethylcarbamyl chloride	107.5	10.0	103 mg	0.96
Lutidine	107.16	20.0	225 $\mu$ L	1.92
DCM			1.5 ml	

[0198] Dimethylcarbamyl chloride (103mg, 0.96mmol) was added to a mixture of deprotected DAP resin (**2**) (125mg, 0.096mmol) and lutidine (225 $\mu$ L, 1.92mmol) in DCM (1.5ml). After shaking at rt for 5 hours, the mixture was drained and washed with DCM (5x2ml), DMF (5x2ml) and DCM (5x2ml). The product was cleaved from the resin through treatment with TFA/water (4:1) (1.5ml). After shaking for 45 min., the TFA solution was collected from the resin by filtration, and the resin was washed with TFA/water (1:1) (2ml). The combined TFA fractions were concentrated under reduced pressure to a reddish-brown solid. The product, identified by LCMS, was purified by prep. HPLC using a 20x50 mm Ultro 120 C18 column running a 22 ml/min 4% gradient (AcCN/water, 0.1% TFA) for 16 min. The purified fractions were lyophilized to dryness. The solid residue was lyophilized again from CH<sub>3</sub>CN/water (1:1) (5ml) give 5 mg of pure product as a white solid (**3**) (~13% yield).

**Example 11: Synthesis of 4'-Ethyl-biphenyl-4-carboxylic acid [2-(2-amino-ethylamino)-1-hydroxycarbamoyl-ethyl]-amide (**2**).**

[0199]



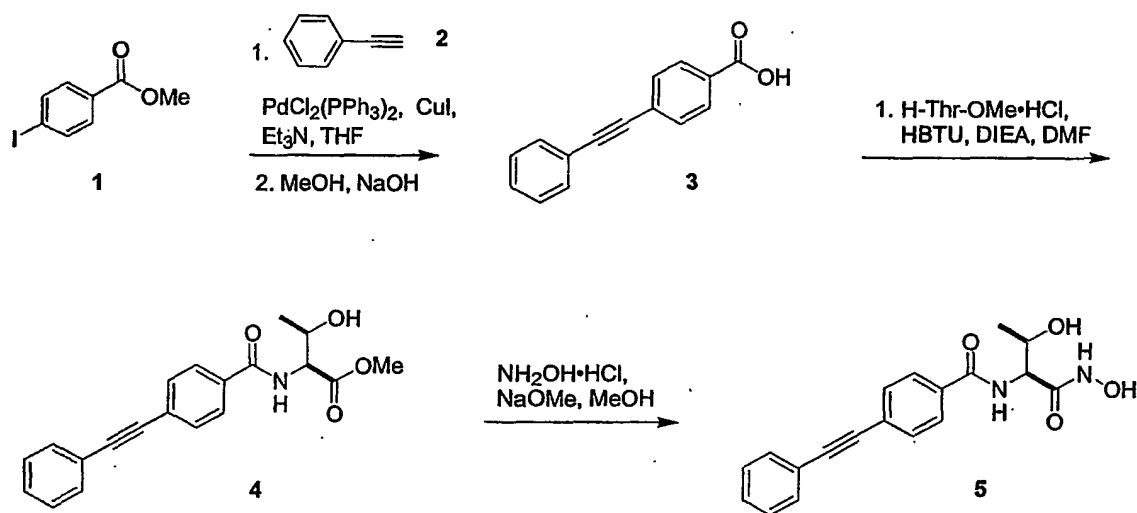
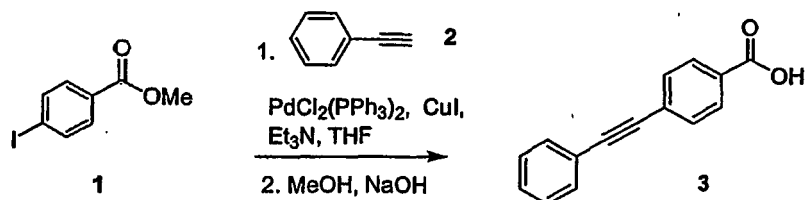
Reagent	MW	EQ	g/ml	mmol
Biphenyl-DAP-hydroxamate ( <b>1</b> )	327.4	1.0	20 mg	0.096

(continued)

Reagent	MW	EQ	g/ml	mmol
Boc-amino-acetaldehyde	159.19	4.0	6.4 mg	0.4
NaBH <sub>3</sub> CN	62.84	10.0	3.1 mg	0.05
Acetic acid	60.05	20.0	6 uL	1.00
DCM			1.5 ml	

**[0200]** NaBH<sub>3</sub>CN (3.1mg, 0.05mmol) followed by acetic acid (6uL, 1.0mmol) were sequentially added to a stirred suspension of biphenyl-DAP-hydroxamate (**1**) (20mg, 0.096mmol) and Boc-amino-acetaldehyde (6.4mg, 0.4mmol) in MeOH (1.5ml) in a 4 ml vial. The reaction was followed by LCMS. After stirring 12 hours, the cloudy reaction was only 50% complete. The reaction was concentrated under reduced pressure to a thick slurry that was dissolved in DMSO. The product was purified by prep. HPLC using a 20x50 mm Ultro 120 C18 column running a 22 ml/min 3% gradient (AcCN/water, 0.1% TFA) for 16 min. The purified fractions were lyophilized to dryness. The dried powder was dissolved in CH<sub>3</sub>CN/water (1:1) (1ml) and 1M HCl (700uL). After heating at 50 °C for 75 min., the reaction mixture was again lyophilized to dryness to produce 7.1 mg of product (**2**) as a 2xHCl salt white powder (~17% yield).

**Example 12: Synthesis of N-(1-(N-hydroxycarbamoyl)(1S,2R)-2-hydroxypropyl)[4-(2-phenylethynyl)phenyl] carboxamide**

**[0201]**Preparation of 4-Phenylethynyl-benzoic acid (**3**)**[0202]**

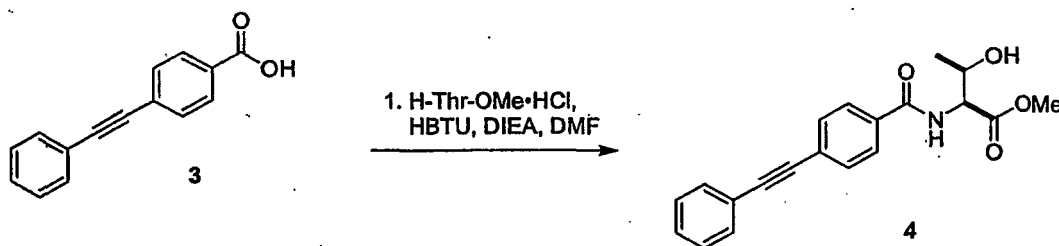
Reagent	MW	EQ	g/ml	mmol
Iodo-benzoate <b>1</b>	262	1.0	20.0 g	76.34
Ethynyl-benzene <b>2</b>	102	1.1	8.56 g	83.96
$\text{PdCl}_2(\text{PPh}_3)_2$	702	0.012	0.65 g	0.92

(continued)

Reagent	MW	EQ	g/ml	mmol	
CuI	190	0.024	0.35 g	1.83	
TEA	101	1.5	16ml	114.5	d=0.726
THF (dry & sparged with argon for 5 min.)			110 ml		

**[0203]** The 4-iodo-benzoic acid methyl ester **1** (20.0g, 76.34mmol), ethynyl-benzene **2** (8.56g, 83.96mmol), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.65g, 0.92mmol), and CuI (0.35g, 1.83mmol) were mixed with THF (110ml) in a round bottom under argon. The dry THF was sparged with dry, oxygen-free argon for at least 5 min. immediately before use. The reaction was cooled to 10 °C and TEA (16ml) was added. The cooling bath was removed and the reaction was stirred at RT under argon. After 2.5h, the reaction was diluted with EtOAc (400 ml) and the solids were filtered off through a pad of celite. The organic filtrate was washed with 1M HCl (60ml), sat. aq. NaHCO<sub>3</sub> (60ml), water (60ml), brine (60ml), dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude solid methyl ester was dissolved in MeOH (400ml), 6M NaOH (30ml) and water (50ml). The reaction was stirred at 70 °C until a clear solution was formed (about 1h). The reaction could be followed by LCMS. The reaction was cooled and diluted with water (500ml) and hexane (100ml). The pH was adjusted to pH 6-7. The white solid that formed was collected and washed with water (3x60ml) and hexane (3x60ml). The solid **3** was dried *in vacuo* yielding 17.3g (approximately quantitative yield in 99% purity).

Preparation of 3-Hydroxy-2-(4-phenylethynyl-benzoylamino)-butyric acid methyl ester (**4**)

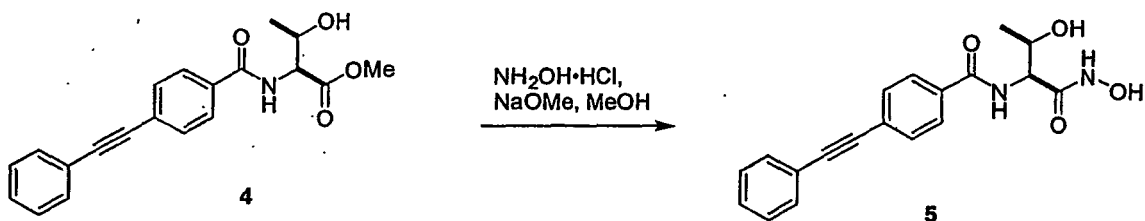
**[0204]**

Reagent	MW	EQ	g/ml	mmol
4-Phenylethynyl-benzoic acid ( <b>3</b> )	222	1.0	1.55 g	7.0
Threonine methyl ester•HCl	169.65	1.4	1.66 g	9.8
HBTU	380	1.0	2.66 g	7.0
DIEA	125.28	2.5	3.05 ml	17.5
DMF			21 ml	

**[0205]** A solution of threonine (1.66g, 9.8mmol) and DIEA (1.53ml, 8.8mmol) in DMF (10ml) was added to a stirred solution of 4-phenylethynyl-benzoic acid **3** (1.55g, 7.0mmol) and DIEA (1.53ml, 8.8mmol) in DMF (11ml) at rt. After 12 h, the reaction was diluted with EtOAc (300ml) and washed with 0.5M HCl (2x60ml), sat. aq. NaHCO<sub>3</sub> (60ml), 50% diluted brine (60ml), sat. brine (60ml), dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Upon drying *in vacuo*, 2.34g of white solid was obtained (approximately quantitative yield in 99% purity).

Preparation of *N*-(2-Hydroxy-1-hydroxycarbonyl-propyl)-4-phenylethynyl-benzamide (**5**)

**[0206]**



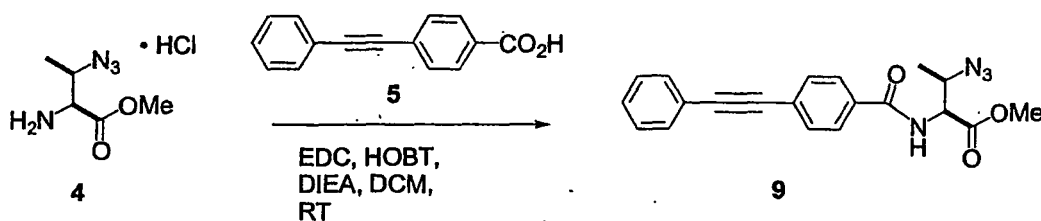
Reagent	MW	EQ	g/ml	mmol
Tolanoic-Thr-OMe (4)	340.42	1.0	2.34 g	7.0
H <sub>2</sub> NOH·HCl	69.49	10.0	4.81 g	70.0
NaOMe	54.02	>11.0	>4.16 g	>77.0
MeOH (dry)			50 ml	
DCM (dry)			30 ml	

[0207] A solution of tolanoic-Thr methyl ester (4) (2.34g, 7.0mmol) in MeOH (20ml) and DCM (30ml) was added to a cooled (-10 °C bath) suspension of hydroxylamine HCl salt (4.81g, 70.0mmol) and NaOMe (4.16g, 77.0mmol) in MeOH (30ml). Follow reaction by LCMS. After stirring for 2 hours, the reaction seems to stall at 50% completion. Add an additional 1 equivalent of NaOMe (0.416g). After 3 hours, the reaction was 75% complete. Add an additional 0.5 equivalent of NaOMe (0.21g). After 4 hours, the reaction was 90% complete. Add an additional 0.15 equivalent of NaOMe (0.064g) for a total of 12.65 equivalents of NaOMe. The pH of the reaction was between 11-12 and had reacted about 95% completion. The reaction was diluted with EtOAc (500ml) and washed with sat. aq. NaHCO<sub>3</sub> (2x60ml), 50% diluted brine (60ml), sat. brine (60ml), dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was dissolved in minimal DMA. The product was purified by prep. HPLC using a reverse phase Ultro 120 C18 column running a 2% gradient (AcCN/water, 0.1% TFA). The purified fractions were lyophilized to dryness. The product as the TFA salt was dissolved in AcCN/water (50:50) (80ml), 1N aq. HCl (13 equivalent) and lyophilized again to give 1.3 g of white powder in 55% yield and >97% purity.

### Example 13: Synthesis of 3-(R)-Amino-2-(S)-(3-phenylethynyl-benzoylamino)-butyl-hydroxamic acid (10)

#### Preparation of 3-(R)-Azido-2-(S)-(3-phenylethynyl-benzoylamino)-butyric acid methyl ester (9).

[0208]



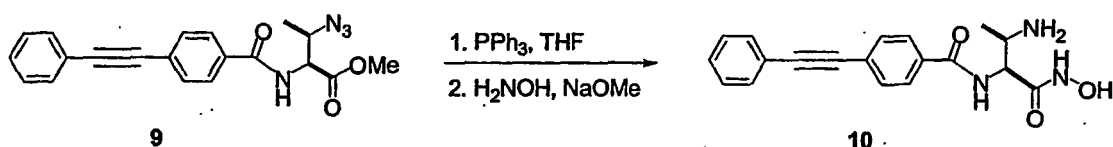
[0209] The synthesis of compound 4 is described above. The tolanyl compound (9) was made by the same procedures as for compound (6). The product (9) was obtained in 92% yield (952mg).

[0210] HPLC(220nm, 41min. run) 32.64 min.; HPLC(220nm, 17min. run) 15.08 min LCMS: LC(214nm) 3.16 min., MS (ES+) m/z 363.1 (C<sub>20</sub>H<sub>18</sub>NaO<sub>3</sub> +H requires 363.14).

#### Preparation of 3-(R)-Amino-2-(S)-(3-phenylethynyl-benzoylamino)-butyl-hydroxamic acid (10)

[0211]





10

Reagent	MW	Eq.	g/ml	mmol
Amino-Thr-OMe (9)	362.38	1.0	726 mg	2.0
PPh <sub>3</sub>	262.29	1.0	526 mg	2.0
H <sub>2</sub> NOH·HCl	69.49	10.0	1.4 g	20.0
NaOMe	54.02	~12.0	1.3 g	24.0
THF(dry)			20 ml	
MeOH(d)y)			20 ml	

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[0212] Triphenylphosphine (526mg, 2.0mmol) was added to a stirred solution of tolanyl-azido-Thr methyl ester (9) (726mg, 2.0mmol) at rt. After 3 days the reaction reached completion as judged by TLC (EtOAc/Hex (2:1)) and LCMS. The reaction was concentrated under reduced pressure to give an ivory colored solid. The crude amino-phosphine was dissolved in MeOH (20ml) to give a pale yellow solution. To the solution of amino-phosphine was added sequentially hydroxylamine HCl salt (1.4g, 20.0mmol) followed by fresh solid NaOMe powder (1.3g, 24.0mmol) to make a milky pH 10 suspension. After 36 h, the reaction was complete by LCMS. The reaction was evaporated under reduced pressure to give a yellow solid that was dried in vacuo. The crude product (2.75g) was triturated with ether (3x50ml) to remove impurities (P(O)Ph<sub>3</sub>) and then was dissolved in abs. EtOH (120ml) with sonication for 15 min.. A fine white powder was suction filtered off, and the clear yellow ethanolic portion was concentrated to a small volume. The crude product was dissolved in DMSO (8ml) and purified by preparative HPLC (Ultron 120 C18 75x300mm column) running a gradient (AcCN/water, 0.1% TFA) from 5 to 70% for 55 min. The purified fractions were pooled together and lyophilized to dryness. The product as the TFA salt was dissolved in AcCN/water (50:50) (100ml), 1N aq. HCl (1 equivalent) and lyophilized again to give 325 mg of light yellow powder as the HCl salt (43% yield).

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[0213] HPLC(220nm, 41min.run) 18.31 min.; HPLC(220nm, 17min.run) 9.11 min; LCMS: LC(214nm) 1.91 min., MS (ES+) m/z 338.1 (C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub> +H requires 338.14).

#### Synthesis of 4'-(N-Acylamino)-Tolan Dap Analogs

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**Example 14: Synthesis of 4-({4-[(aminoacetyl)amino]phenyl}ethynyl)-N-[(1S)-1-(aminomethyl)-2-(hydroxyamino)-2-oxoethyl]benzamide**

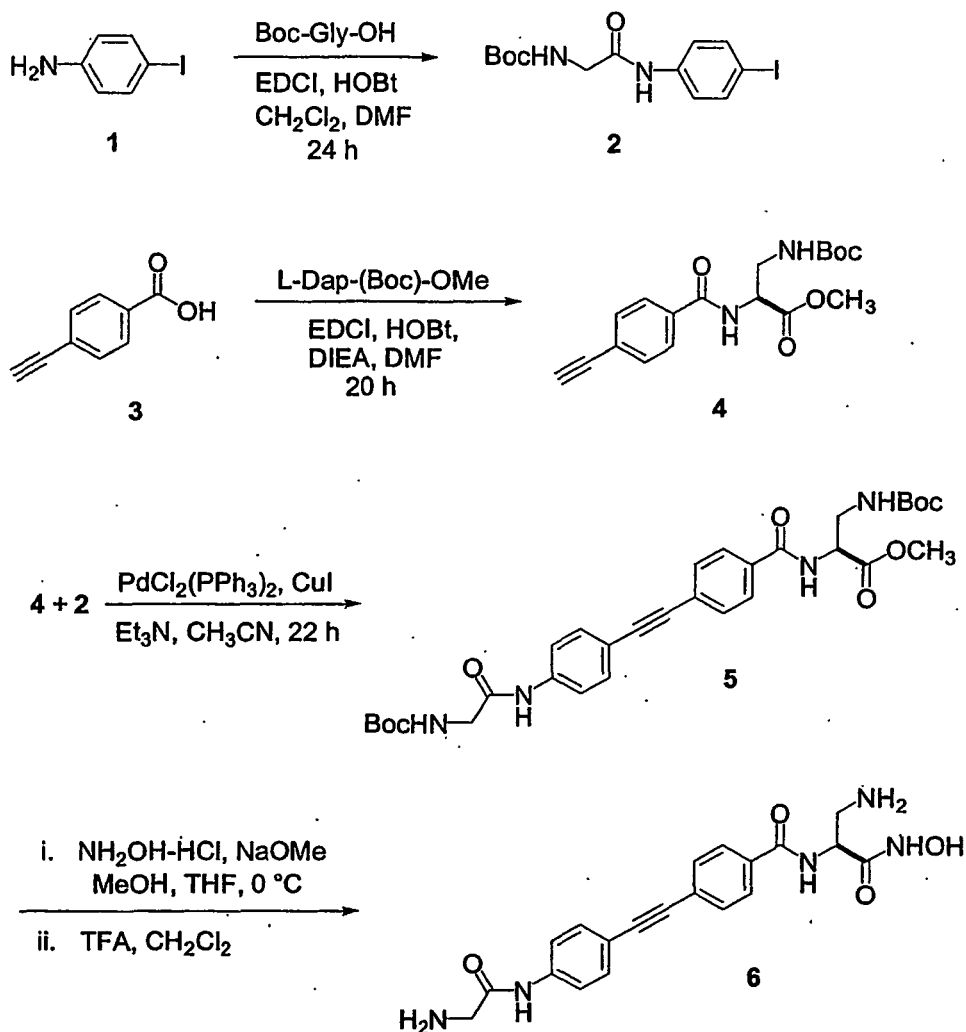
[0214]

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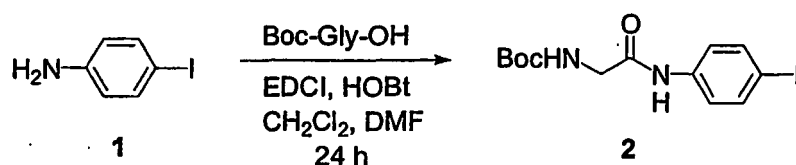
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**Preparation of 2-N-Boc-amino-N-(4-iodo-phenyl)-acetamide (2).**

[0215]



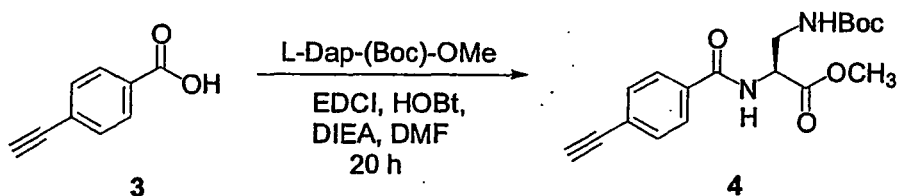
Reagent	MW	Eq.	g/ml	mmol
Boc-Gly-OH	175.19	1.00	1.752 g	10.0
4-Iodoaniline (1)	219.03	1.04	2.290 g	10.4
EDCI	191.71	1.04	1.994 g	10.4
HOBT	135.13	1.00	1.351 g	10.0
DCM			18 mL	
DMF			1 mL,	

**[0216]** A solution of Boc-Gly-OH (1.752 g, 10.0 mmol) in DCM (18 mL) and DMF (1 mL) was treated with EDCI (1.994 g, 10.4 mmol) and HOBT (1.351 g, 10.0 mmol). After stirring 15 min, 4-iodoaniline 1 (2.290 g, 10.4 mmol) was added

and the reaction monitored by TLC (25:1 DCM/MeOH ( $R_f = 0.6$ )). After 24 h the solution was diluted with EtOAc (250 mL), washed with 1.0 M HCl ( $3 \times 100$  mL), sat.  $\text{NaHCO}_3$  ( $3 \times 100$  mL), brine ( $3 \times 100$  mL), dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to afford 2.900 g (77% yield) of a white solid.

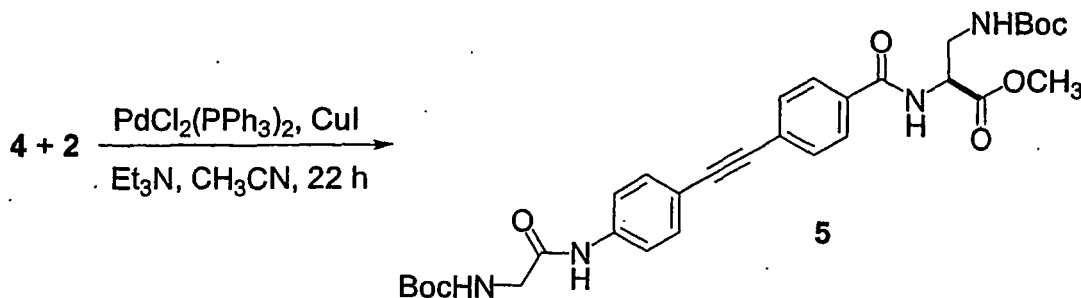
#### Preparation of (2S)-3-N-Boc-amino-(4-ethynyl-benzoylamino)-propionic acid methyl ester (4).

[0217]



Reagent	MW	Eq.	g/mL	mmol
4-Ethynylbenzoic acid (3)	146.14	1.0	0.910 g	6.22
H-Dap(Boc)-OMe-HCl	254.71	1.2	1.903 g	7.47
EDCI	191.71	1.2	1.432 g	7.47
HOBT	135.13	1.1	0.910 g	6.73
DIEA	129.25	3.2	3.5 mL	20.0
DMF			50 mL	

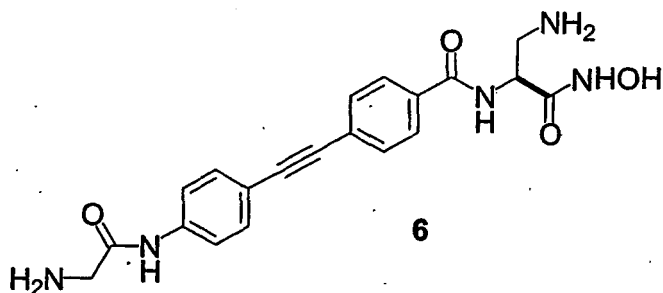
[0218] Triethylamine (3.5 mL, 20.0 mmol) was added to a stirred solution of 4-ethynylbenzoic acid 3 (910 mg, 6.22 mmol), H-Dap(Boc)-OMe hydrochloride (1.903 g, 7.47 mmol), EDCI (1.432 g, 7.47 mmol), and HOBT (910 mg, 6.73 mmol) in DMF (50.0 mL). After stirring 20 h, the reaction mixture was diluted with EtOAc (400 mL), washed with 1.0 M HCl ( $2 \times 100$  mL), saturated  $\text{NaHCO}_3$  ( $2 \times 100$  mL),  $\text{H}_2\text{O}$  ( $4 \times 100$  mL), dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to give 2.140 g (99% yield) of a tan solid, mp = 110-111 °C. LRMS (ES+)  $m/z$  346.9 ( $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_5 + \text{H}$  requires 347.10).



[0219] To a suspension of methyl (2S)-3-[(tert-butoxy)carbonylamino]-2-[(4-ethynylphenyl)carbamoyl]propanoate (4) (200 mg, 0.577 mmol) and 2-[(tert-butoxy)carbonylamino]-N-(4-iodophenyl)acetamide (2) (476 mg, 1.26 mmol) was added  $\text{Et}_3\text{N}$  (350  $\mu\text{L}$ , 2.5 mmol). The solution was purged with a stream of  $\text{N}_2$  for several minutes and  $\text{PdCl}_2(\text{PPh}_3)_2$  (20 mg, 0.028 mmol) and  $\text{CuI}$  (10.6 mg, 0.055 mmol) were added. The reaction mixture was stirred at ambient temperature for 22 h and then concentrated by rotary evaporation. The crude black residue was chromatographed twice by silica gel chromatography (30:1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ) to give 285 mg (83%) of methyl (2S)-3-[(tert-butoxy)carbonylamino]-2-[(4-ethynylphenyl)carbamoyl]propanoate (5) as a yellow foam.

i.  $\text{NH}_2\text{OH}\cdot\text{HCl}$ , NaOMe  
MeOH, THF, 0 °C

ii. TFA,  $\text{CH}_2\text{Cl}_2$

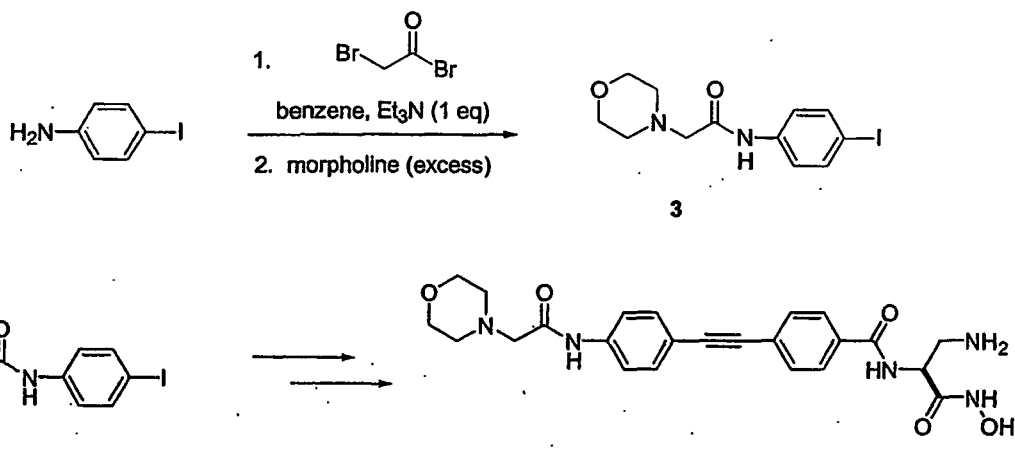


**[0220]** To a solution of hydroxylamine hydrochloride (98 mg, 1.41 mmol) in MeOH (1.3 mL) at 0 °C was added 25 wt% NaOMe (460 mg, 2.13 mmol). The solution was stirred at 0 °C for 15 min and then charged with a solution of methyl (2S)-3-[(tert-butoxy)carbonylamino]-2-[(4-[2-(4-{2-[(tert-butoxy)carbonylamino]acetamino} phenyl)ethynyl]phenyl) carbonylamino] propanoate (4) (279 mg, 0.469 mmol) in THF (1.5 mL) and MeOH (0.6 mL). The reaction was stirred at 0 °C for 30 min and at room temperature for 2.5 h. The reaction mixture was diluted with 4:1  $\text{CHCl}_3/\text{iPrOH}$  (50 mL) and washed with 0.1 M HCl (30 mL). The layers were separated and the aqueous layer extracted once more with 4:1  $\text{CHCl}_3/\text{iPrOH}$  (30 mL). The organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The crude residue was suspended in 10:1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (4 mL), filtered, and washed with 50:1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (2 mL) and  $\text{Et}_2\text{O}$  (10 mL) to afford 180 mg (64%) of N-(4-{2-(4-(N-{1-(N-hydroxycarbonyl)(1S)-2-[(tert-butoxy)carbonylamino]ethyl) carbamoyl} phenyl)ethynyl}phenyl)-2-[(tert-butoxy)carbonylamino]acetamide (**6**) as a white powder.

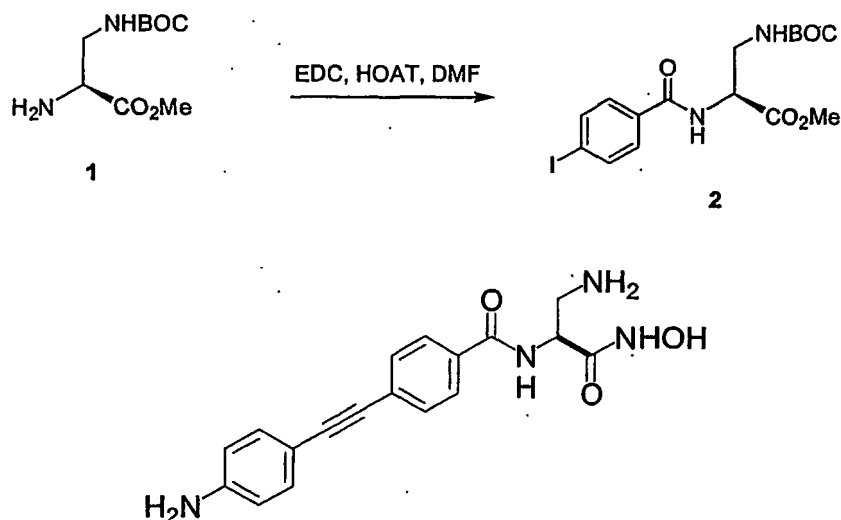
**[0221]** To an oven-dried flask containing N-(4-{2-(4-(N-{1-(N-hydroxycarbonyl)(1S)-2-[(tert-butoxy)carbonylamino]ethyl) carbamoyl} phenyl)ethynyl}phenyl)-2-[(tert-butoxy)carbonylamino]acetamide (**6**) (130 mg, 0.218 mmol) was added 1:1 TFA/ $\text{CH}_2\text{Cl}_2$  (2.5 mL). The resulting pink solution was stirred for 2 h and concentrated to give a pink gum. The crude residue was rinsed with  $\text{CH}_2\text{Cl}_2$  (4 mL), concentrated by rotary evaporation and dissolved in THF (2 mL) and MeOH (0.4 mL). A solution of 4 M HCl in dioxane (200  $\mu\text{L}$ ) was added and the resulting precipitate filtered and washed with  $\text{Et}_2\text{O}$  (10 mL) to afford 90 mg of 4-{4-[(aminomethyl)amino]phenyl}ethynyl)-N-[(1S)-1-(aminomethyl)-2-(hydroxyamino)-2-oxoethyl]benzamide as a pale tan powder.

#### Reaction of Iodoaniline with Bromoacetyl Bromide

**[0222]**



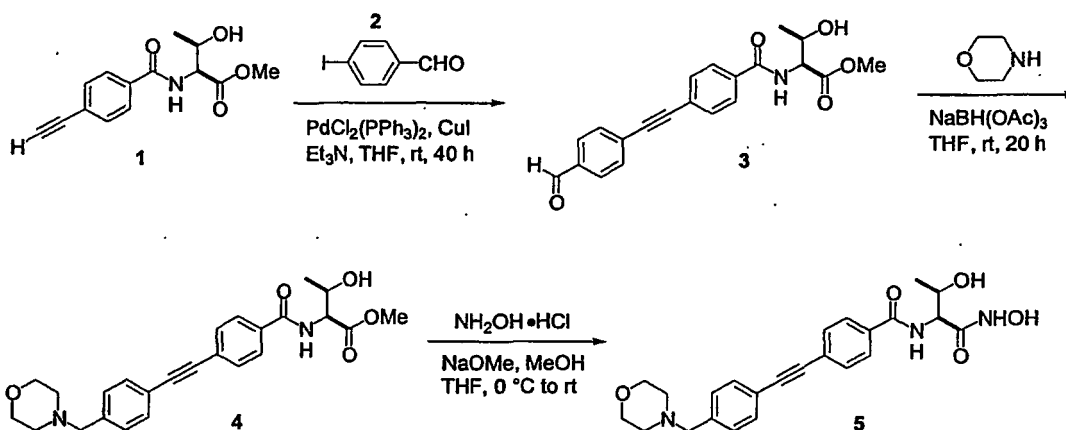
**[0223]** Bromoacetyl bromide (175  $\mu\text{L}$ , 2.00 mmol) was added dropwise over 5 minutes to a solution of 4-iodoaniline (438 mg, 2.00 mmol) and  $\text{Et}_3\text{N}$  (280  $\mu\text{L}$ , 2.00 mmol) in benzene (5 mL). The reaction was stirred 1 hour, treated with morpholine (1.0 mL, 11.5 mmol) and stirred overnight. The reaction mixture was diluted with  $\text{EtOAc}$  (200 mL), washed with aqueous 0.1 M KOH (50 mL),  $\text{H}_2\text{O}$  (50 mL), dried over  $\text{MgSO}_4$  and concentrated to give a yellow oil. Purification by silica gel chromatography (100:1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ) afforded 630 mg (91%) of N-(4-iodophenyl)-2-morpholin-4-ylacetamide as a waxy tan solid. This product was converted to analogues in a similar manner as Example 14.

**Example A: Preparation of 4-[4-(6-Chloro-pyridin-3-yl)-buta-1,3-diynyl]-benzoic acid methyl ester.****[0224]**

Reagent	MW	EQ	g/ml	mmol
H-DAP(Boc)-OMe (1)	254	1.05	5.93 g	23.3
4-Iodo-benzoic acid	248	1.0	5.49 g	22.2
HOAT	136.1	1.02	3.08 g	22.6
EDC	191.71	1.02	4.33g	22.6
DIEA	129.25	2.5	9.7 ml	55.1
DMF			85 ml	

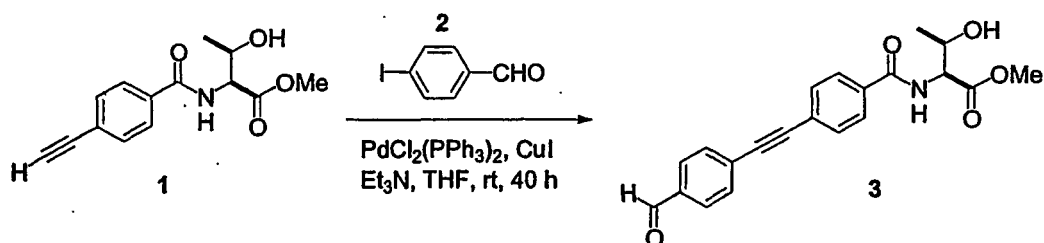
**[0225]** DIEA (9.7ml, 55.1mmol) was added to a stirred solution of 4-iodo-benzoic acid (5.49g, 22.2mmol), HOAT (3.08g, 22.6mmol), EDC (4.33g, 22.6mmol) in DMF (85ml). After 2 min., the H-DAP(Boc)-OMe (1) was added in one portion. After 12 hours, the reaction was found complete by LCMS. The reaction was diluted with EtOAc/hexane (1:1) (500ml). The organic phase was washed with 1N HCl (2x80ml), 1N NaOH (2x80ml), water (2x80ml), sat. brine (80ml), dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product. The residue was filtered through a filter plug of silica eluting with EtOAc/hexane (1:1). The fractions with product were evaporated to give 9.3 g of product (3-tert-Butoxycarbonylamino-2-(4-iodo-benzoylamino)-propionic acid methyl ester) in 93% yield. This product was converted to analogues in a similar manner as the aforementioned Examples.

**Example 15: N-(1-(N-hydroxycarbamoyl)(1S,2R)-2-hydroxypropyl)(4-{2-[4-(morpholin-4-ylmethyl)phenyl]ethynyl}phenyl)carboxamide (5)****[0226]**



Preparation of (2S, 3R)-2-[4-(4-formyl-phenylethynyl)-benzoylamino]-3-hydroxy-butyric acid methyl ester (3).

[0227]

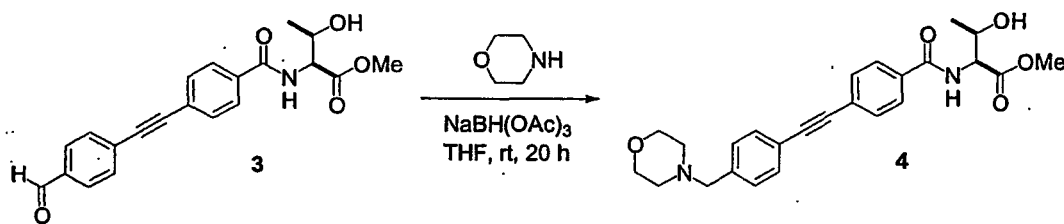


Reagent	MW	Eq.	g/ml	mmol
Ethynylbenzene (1)	261.27	1.0	0.745 g	2.85
4-Iodobenzaldehyde (2)	232.00	1.4	0.902 g	3.89
$\text{PdCl}_2(\text{PPh}_3)_2$	701.89	0.03	0.070 g	0.10
CuI	190.44	0.06	0.034 g	0.18
$\text{Et}_3\text{N}$	101.19	2.3	0.90 mL	6.5
THF			50 mL	

[0228] A solution of alkyne 1 (745 mg, 2.85 mmol), 4-iodobenzaldehyde 2 (902 mg, 3.89 mmol), and  $\text{Et}_3\text{N}$  (900  $\mu\text{L}$ , 6.5 mmol) in THF (50 mL) was purged with a stream of  $\text{N}_2$  for two minutes and then treated with  $\text{PdCl}_2(\text{PPh}_3)_2$  (70 mg, 0.10 mmol) and CuI (34 mg, 0.18 mmol). The reaction mixture was stirred 40 h, concentrated by rotary evaporation and purified by silica gel chromatography (40:1 DCM/MeOH) to give 0.833 g (80% yield) of (2S, 3R)-2-[4-(4-formyl-phenylethynyl)-benzoylamino]-3-hydroxy-butyric acid methyl ester 3 as a pale yellow powder, mp = 143-144 °C.  $R_f$  = 0.3 (25:1 DCM/MeOH); LRMS (ES+)  $m/z$  366.1 ( $\text{C}_{21}\text{H}_{19}\text{NO}_5 + \text{H}$  requires 366.13); HPLC (300 nm, 47 min) 15.3 min.

Preparation of (2S, 3R)-3-Hydroxy-2-[4-(4-morpholin-4-ylmethyl-phenylethynyl)-benzoylamino]-butyric acid methyl ester (4).

[0229]

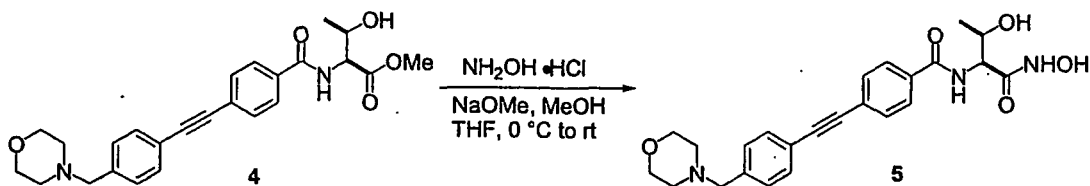


Reagent	MW	Eq.	g/ml	mmol
Tolanylaldehyde ( <b>3</b> )	365.38	1.0	0.822 g	2.25
Morpholine	87.12	1.3	0.260 mL	2.97
$\text{NaBH}(\text{OAc})_3$	211.94	1.4	0.670 g	3.16
THF			15 ml	

**[0230]** Sodium triacetoxyborohydride (0.670 g, 3.16 mmol) was added to a solution of benzaldehyde **3** (0.822 g, 2.25 mmol) and morpholine (260  $\mu\text{L}$ , 2.97 mmol) in THF (15 mL) under  $\text{N}_2$  atmosphere and the reaction monitored by TLC (25:1 DCM/MeOH,  $R_f=0.2$ ). After stirring 4 h, the reaction mixture was quenched with saturated  $\text{NaHCO}_3$  (150 mL), extracted with EtOAc ( $3 \times 100$  mL), dried over  $\text{MgSO}_4$ , filtered and concentrated to give a yellow syrup. Purification by silica gel chromatography (35:1 DCM/MeOH) afforded 0.844 g (86% yield) of **4** as a sticky white foam.

**Preparation of (2S, 3R)-N-(2-Hydroxy-1-hydroxycarbamoyl-propyl)-4-(4-morpholin-4-ylmethyl-phenylethynyl)-benzamide (5).**

**[0231]**



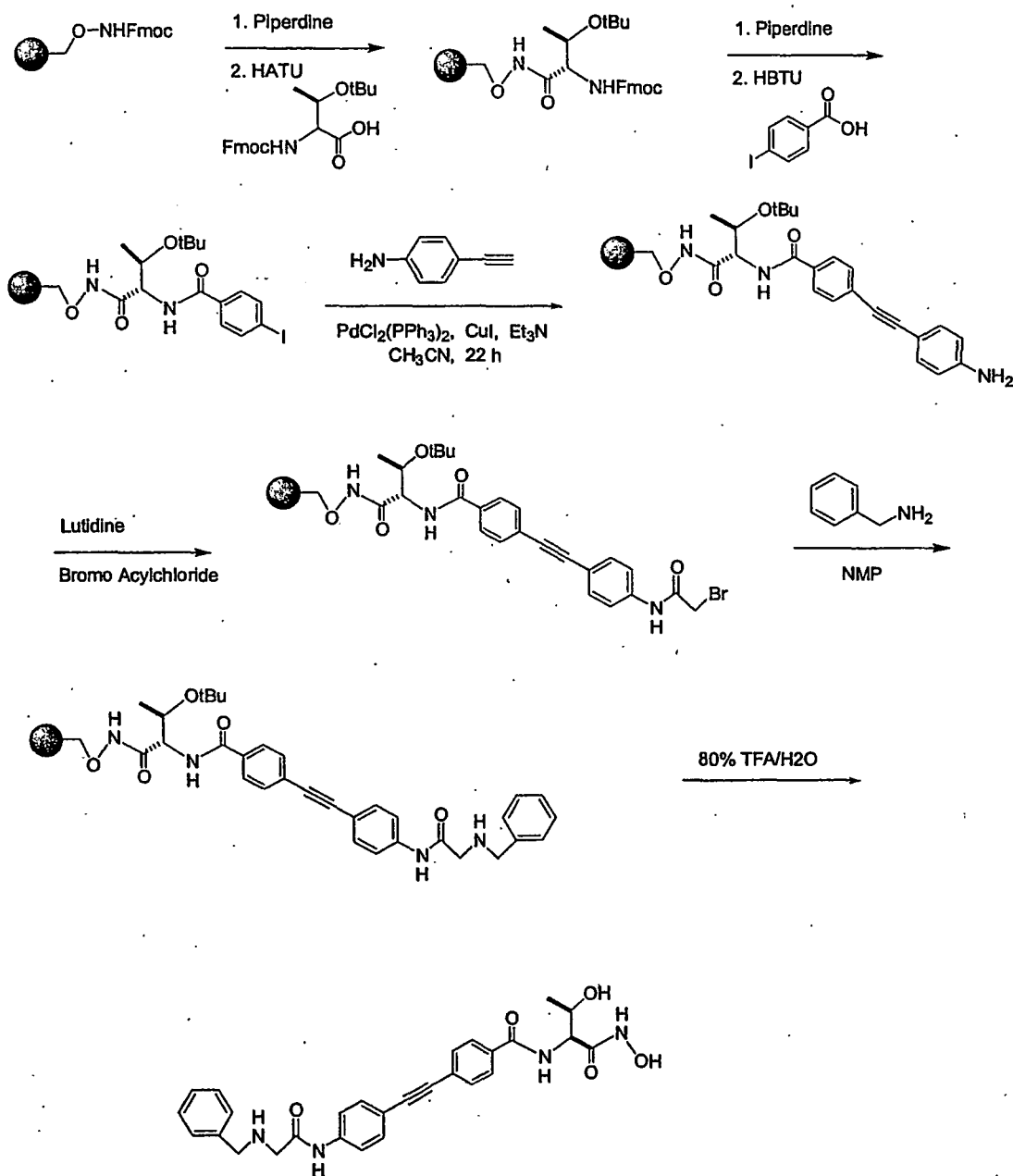
Reagent	MW	Eq.	g/ml	mmol
Methyl ester ( <b>4</b> )	436.50	1.0	0.829 g	1.90
$\text{NH}_2\text{OH} \cdot \text{HCl}$	69.49	3.0	0.400 g	5.76
$\text{NaOMe}$ (25 wt%)	54.02	4.5	1.860 g	8.60
MeOH			8 mL	
THF			3 mL	

**[0232]** Sodium methoxide (25 wt% in MeOH, 1.860 g, 8.60 mmol) was added to a stirred solution of hydroxylamine hydrochloride (400 mg, 5.76 mmol) in anhydrous MeOH (5 mL) at  $0^\circ\text{C}$  under  $\text{N}_2$  atmosphere. After stirring 20 min, a solution of methyl ester **4** (829 mg, 1.90 mmol) in 1:1 MeOH/THF (6 mL) was added and the reaction mixture stirred at  $0^\circ\text{C}$  for 1 h and at room temperature for 4 h. The reaction was quenched with 1.0 M HCl (6 mL), concentrated by rotary evaporation to remove organic solvents, and diluted with DMSO (4 mL). Analytical RP-HPLC ( $\text{C}_{18}$  column,  $\text{CH}_3\text{CN}$  gradient 5-35%, 0.1 % TFA, UV analysis 300 nm, 16 min) indicated a purity of 85% for the crude product mixture. Purification by preparative RP-HPLC and lyophilization of the collected fractions gave 701 mg (81%) of **5** as a fluffy white solid. LRMS ( $\text{ES}^+$ )  $m/z$  438.1 ( $\text{C}_{24}\text{H}_{27}\text{N}_3\text{O}_5 + \text{H}$  requires 438.20); RP-HPLC (300 nm, 16 min run) 8.7 min.

## Resin Procedures for Synthesizing Tolanyl hydroxamates

**Example 16: Synthesis of 4-[(4-[(benzylamino)acetyl]amino} phenyl)ethynyl]-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino) carbonyl]propyl]benzamide**

[0233]



## 1. Coupling to Fmoc hydroxylamine resin

**[0234]** The resin was pre-swelled by adding DCM and shaking for 30min. The resin was drained, 20% piperidine was added in DMF, the resin was shaken 1.25 hours, and finally drained and washed in 2xDMF and 2xDCM. After draining completely, 20% piperidine in DMF was added to attain cleavage in 1.25 hours. The resin was washed 4xDMF, 4xDCM and drained completely. In a separate flask, the amino acid (Fmoc-Thr tBu-OH, or Fmoc-DAP Boc-OH, 4 eq) was mixed, HATU (4 eq), DMF (60 ml) and Hunig's (8 eq) base were added and stirred for 2-3 min. The mixture was added to the resin and shaken 20-24 hours. Subsequently, the resin was drained and run with a standard wash (1xDCM, 4xDMF and



4xDCM). The Fmoc was removed from the amino acid by adding 20% piperidine in DMF and shaken 1.25 hours, drained, and given the standard wash (1xDCM, 4xDMF and 4xDCM).

## 2. Coupling of 4-iodobenzoic acid to Amino Acid resin

**[0235]** A mixture of 4-iodobenzoic acid (4 eq), HBTU (4 eq), DMF (60 ml) was shaken for several minutes. Hünig's base (8 eq) was subsequently added and the mixture was shaken further for 2-3 min. The pre-activated mixture was then added to the prepared Thr or DAP resin (Fmoc removed, 7.5g, 5.775 mmol). The reaction is shaken 12-16 hours followed by the standard wash (1xDCM, 4xDMF and 4xDCM).

## 3. Alkyne coupling on Resin

**[0236]** To the 4-iodobenzoic resin (4 g, 3.08 mmol) was added 4-aminophenylacetylene (3 eq), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (0.04 eq), Cul (0.08 eq) and THF (purged with Argon). After mixing for 1 min., TEA (4.5 eq) was added and the reaction was shaken 12 hours at RT under argon.

## 4. Aniline coupling with bromoacetyl chloride on Resin

**[0237]** To aniline resin (4g, 3.08 mmol) was added DCM (30 ml) lutidine (10 eq) and shaken for 1 min. Bromoacetyl chloride (8 eq) in DCM (5 ml) was added slowly. After the addition, the slurry was shaken for 1.5 to 1.75 hours. Subsequent draining and a wash with 2xDCM, 4xDMF and 4xDCM was then performed.

## 5. Displacement with amines on Resin

**[0238]** To the bromoacetyl resin (125 mg), was added NMP (1.5 ml) followed by amine (0.2 g or ml, ie excess) and the slurry was shaken for 12-16 hours at RT. To neutralize the salt, TEA was added. The imidazole was heated at 38 °C for 24 h (in the case of anilines, they were heated at 38 °C for 48 h). The reaction mixture was drained and washed 4xDMF and 4xDCM.

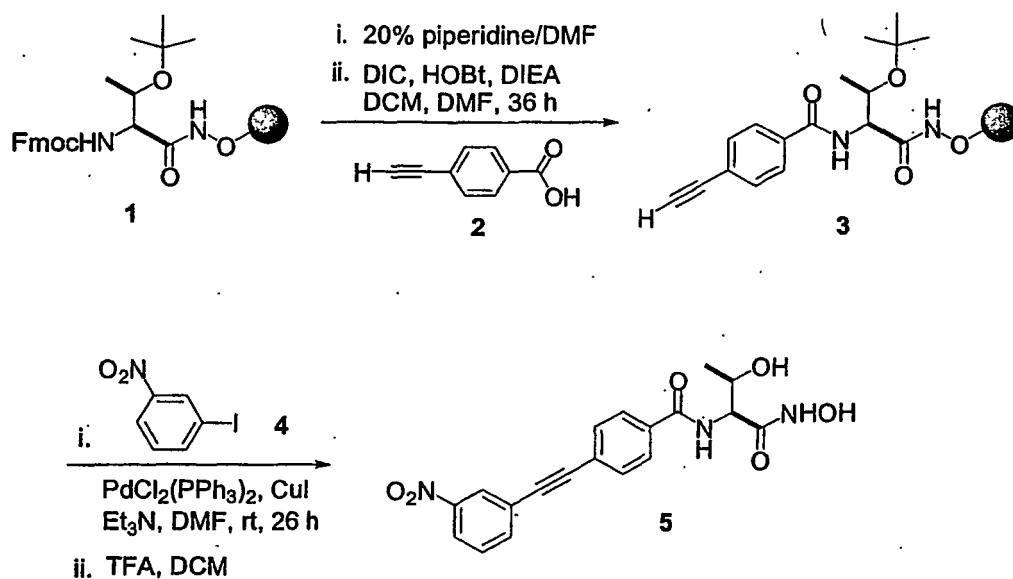
## 6. Cleavage from resin and deprotection of Thr tBu and DAP Boc

**[0239]** The resin (125 mg) was soaked in TFA/water (80:20 v/v) (1.5 ml) at RT for 45 min. Upon cleavage the solution was collected and the resin was washed with more TFA/water mixture (0.75 ml). To the TFA/product solution was added acetonitrile/water solution (1:1 v/v, 10 ml) and pure water (2.5 ml). The mixture was frozen in liquid nitrogen for ~15 min and lyophilized. The dry residue was dissolved in the acetonitrile/water solution (1:1 v/v, 10 ml) again followed by addition of 1M aq. HCl (1.2 eq per basic nitrogen), frozen, and lyophilized to a powder.

## Synthesis of 3'-Nitro-Tolan Threonine Hydroxamic Acid

### Example 17: (1S,2R)- N-(2-hydroxy-1-hydroxycarbonyl-propyl)-4-(3-nitro-phenylethynyl)-benzamide

**[0240]**



**Preparation of (1S,2R)-N-(2-tert-butoxy-1-hydroxycarbamoyl-propyl)-4-ethynyl-benzamide on hydroxylamine 2-chlorotrityl resin (3).**

[0241]

Reagent	MW	Eq.	g/mL	mmol
Fmoc-threonine/resin (1)	0.70 mmol/g	1.0	0.522 g	0.365
4-Ethynylbenzoic acid (2)	146.14	3.0	0.160 g	1.10
DIC	126.20	4.9	0.28 mL	1.79
HOBt	135.13	3.0	0.148 g	1.10
DIEA	129.25	6.3	0.40 mL	2.30
DCM			1.0 mL	
DMF			3.0 mL	

[0242] The resin 1 (0.522 g, 0.365 mmol, 0.70 mmol/g) was swelled in DCM (5 mL) for 2 h and drained. The resin was treated with 20% piperidine in DMF (6 mL) for 1 hour, washed with DMF (4 × 6 mL) and DCM (4 × 6 mL) and drained completely. In a separate flask, 4-ethynylbenzoic acid 2 (0.160 g, 1.10 mmol), DIC (0.280 mL, 1.79 mmol), HOBt (0.148 g, 1.10 mmol) and DIEA (0.4 mL, 2.30 mmol) were dissolved in DCM (1 mL) and DMF (4 mL), stirred 15 min and added to the resin. After shaking for 36 h, the mixture was drained, washed with DMF (4 × 6 mL) and DCM (4 × 6 mL) and dried *in vacuo* to give 0.495 g of a yellow resin.

**Preparation of (1S,2R)-N-(2-hydroxy-1-hydroxycarbamoyl-propyl)-4-(3-nitro-phenylethynyl)-benzamide (5).**

[0243]

Reagent	MW	Eq.	g/mL	mmol
Alkyne on resin (3)	0.70 mmol/g	1.0	100 mg	0.070
1-Iodo-3-nitrobenzene (4)	249.01	5.0	87.1 mg	0.350
PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	701.89	0.2	10.0 mg	0.014
CuI	190.44	0.5	7.0 mg	0.036
Et <sub>3</sub> N	101.19	15	150 μL	1.10
DMF			1.5 mL	

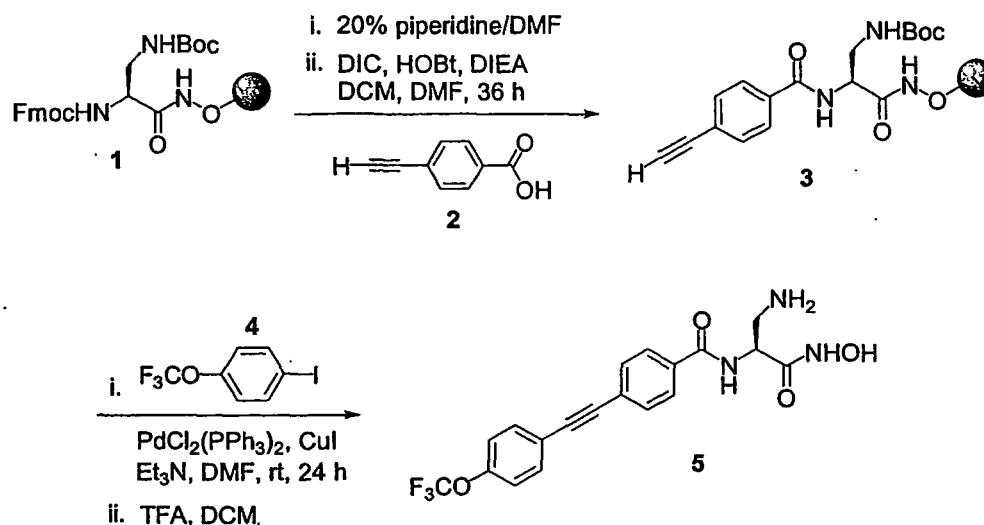
[0244] Resin 3 (100 mg, 0.070 mmol) was swelled in DCM (2 mL) for 1 h and drained. A solution of 1-iodo-3-nitrobenzene 4 (87.1 mg, 0.350 mmol) and Et<sub>3</sub>N (150 μL, 1.10 mmol) in DMF (1.5 mL) was purged with a stream of N<sub>2</sub> bubbles for

two minutes and added to the resin. After mixing for 5 min,  $\text{PdCl}_2(\text{PPh}_3)_2$  (10.0 mg, 0.014 mmol) and  $\text{CuI}$  (7.0 mg, 0.036 mmol) were added and the mixture shaken for 26 h. The resin was drained, washed with DMF (3 x 2 mL), DCM (3 x 2 mL) and cleaved with 10% TFA/DCM (1.5 mL) for 20 min. The solution was collected and the resin was rinsed with additional 10% TFA/DCM (1.0 mL). The cleavage fractions were combined, treated with neat TFA (2.0 mL), stirred for 1 h at rt and concentrated by rotary evaporation to give a crude brown residue. Purification by RP-HPLC ( $\text{C}_{18}$  column,  $\text{CH}_3\text{CN}$  gradient 5-65%, 0.1% TFA, UV analysis 300 nm, 28 min) and lyophilization of the collected fractions afforded 6.0 mg (22% yield) of (1S,2R)-N-(2-hydroxy-1-hydroxycarbamoyl-propyl)-4-(3-nitro-phenylethynyl)-benzamide as a white foam. LRMS (ES+)  $m/z$  384.2 ( $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_6 + \text{H}$  requires 384.15); RP-HPLC (300 nm, 28 min run) 15.2 min.

#### Synthesis of 4'-Trifluoromethoxy-Tolan Dap Hydroxamic Acid

**Example 18: (1S)-N-(2-amino-1-hydroxycarbamoyl-ethyl)-4-(4-trifluoromethoxy-phenylethynyl)-benzamide (5)**

[0245]



**Preparation of (1S)-N-(2-(Boc)-amino-1-hydroxycarbamoyl-ethyl)-4-ethynyl-benz-amide on hydroxylamine 2-chlorotrityl resin (3).**

[0246]

Reagent	MW	Eq.	g/mL	mmol
Fmoc-Dap/resin (1)	0.70 mmol/g	1.0	1.330 g	0.931
4-Ethynylbenzoic acid (2)	146.14	3.0	0.408 g	2.793
DIC	126.20	4.8	0.70 mL	4.470
HOBT	135.13	3.0	0.377 g	2.793
DIEA	129.25	6.2	1.0 mL	5.7
DCM			10.0 mL	
DMF			2.0 mL	

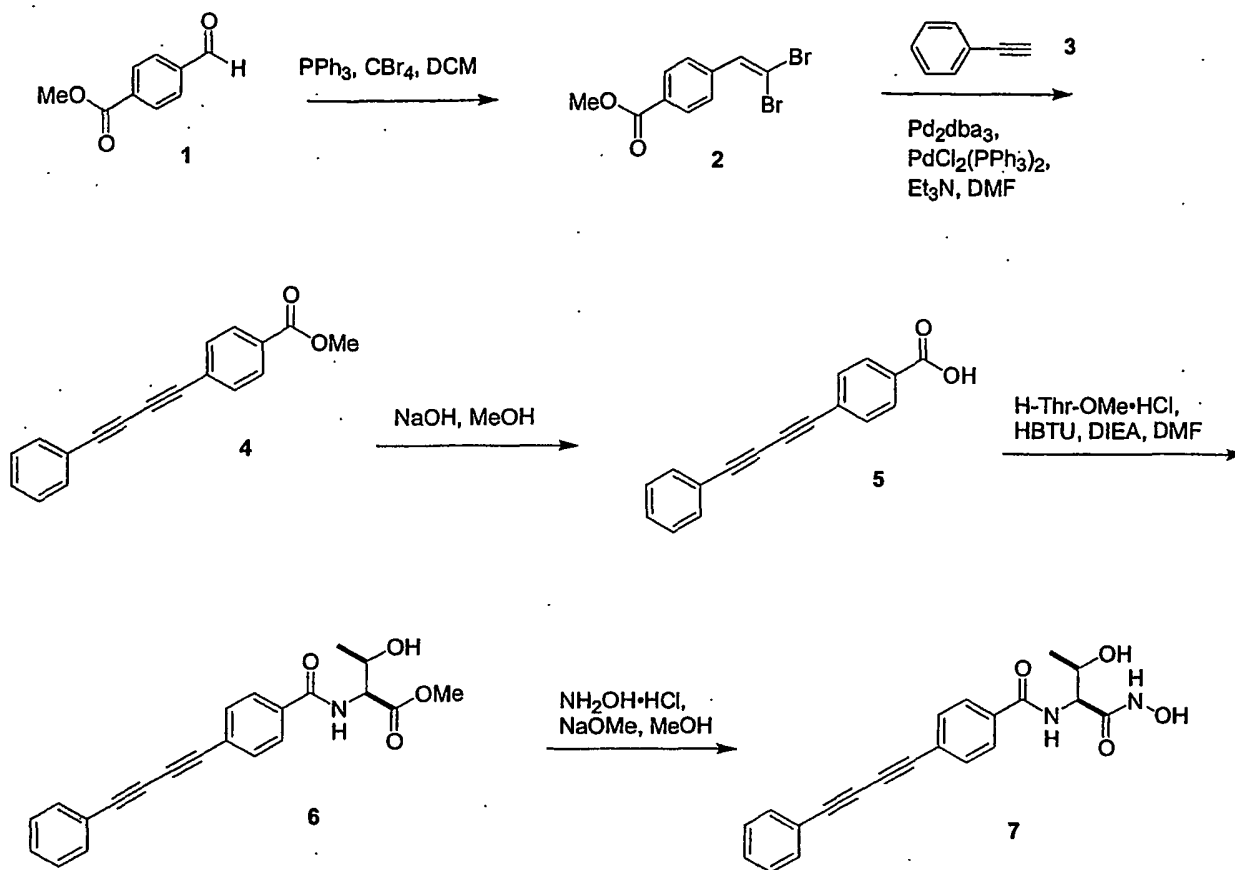
[0247] The resin 1 (1.330 g, 0.931 mmol, 0.70 mmol/g) was swelled in DCM (15 mL) for 2 h and drained. The resin was treated with 20% piperidine in DMF (20 mL) for 1 hour, washed with DMF (3 x 15 mL) and DCM (3 x 15 mL) and drained completely. In a separate flask, 4-ethynylbenzoic acid 2 (0.408 g, 2.793 mmol), DIC (0.70 mL, 4.470 mmol), HOBT (0.377 g, 2.793 mmol) and DIEA (1.0 mL, 5.7 mmol) were dissolved in DCM (10 mL) and DMF (2 mL), stirred 15 min and added to the resin. After shaking for 36 h, the mixture was drained, washed with DMF (3 x 15 mL) and DCM (3 x 15 mL) and dried *in vacuo* to give 1.290 g of a yellow resin.

**Preparation of (1S)-N-(2-amino-1-hydroxycarbamoyl-ethyl)-4-(4-trifluoromethoxy-phenylethynyl)-benzamide (5).****[0248]**

Reagent	MW	Eq.	g/mL	mmol
Alkyne on resin ( <b>3</b> )	0.70 mmol/g	1.0	120 mg	0.084
4-CF <sub>3</sub> O-iodobenzene ( <b>4</b> )	287.99	4.0	96.8 mg	0.336
PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	701.89	0.3	18.0 mg	0.025
CuI	190.44	0.5	8.0 mg	0.042
Et <sub>3</sub> N	101.19	13	150 $\mu$ L	1.10
DMF			2.0 mL	

**[0249]** Resin **3** (120 mg, 0.084 mmol) was swelled in DCM (2 mL) for 1 h and drained. A solution of 4-(trifluoromethoxy) iodobenzene **4** (96.8 mg, 0.336 mmol) and Et<sub>3</sub>N (150  $\mu$ L, 1.10 mmol) in DMF (2.0 mL) was purged with a stream of N<sub>2</sub> bubbles for two minutes and added to the resin. After mixing for 5 min, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (18.0 mg, 0.025 mmol) and CuI (8.0 mg, 0.042 mmol) were added and the mixture shaken for 24 h. The resin was drained, washed with DMF (3  $\times$  2 mL), DCM (3  $\times$  2 mL) and cleaved with 10% TFA/DCM (2.0 mL) for 20 min. The solution was collected and the resin was rinsed with additional 10% TFA/DCM (1.0 mL). The cleavage fractions were combined, treated with neat TFA (3.0 mL), stirred for 1 h at rt and concentrated by rotary evaporation to give a crude brown residue. Purification by RP-HPLC (C<sub>18</sub> column, CH<sub>3</sub>CN gradient 5-55%, 0.1% TFA, UV analysis 300 nm, 28 min) and lyophilization of the collected fractions afforded 9.0 mg (25% yield) of (1S)-N-(2-amino-1-hydroxycarbamoyl-ethyl)-4-(4-trifluoromethoxy-phenylethynyl)-benzamide as a white solid. LRMS (ES<sup>+</sup>) *m/z* 408.0 (C<sub>19</sub>H<sub>16</sub>F<sub>3</sub>N<sub>3</sub>O<sub>4</sub> + H requires 408.11); RP-HPLC (300 nm, 28 min run) 18.0 min.

**Example 19: Synthesis of N-(1-(N-hydroxycarbamoyl)(1S,2R)-2-hydroxypropyl)[4-(4-phenylbuta-1,3-diynyl) phenyl]carboxamide****[0250]**



Reagent	MW	EQ	g/ml	mmol
Dibromovinylbenzoic acid (2)	320	1.0	5.76 g	18.0
Ethynyl-benzene	102	1.4	2.57 g	25.2
Pd <sub>2</sub> dba <sub>3</sub>	915	0.01	164 mg	0.18 (1% cat.)
TMPP	352	0.04	253 mg	0.72 (4%)
TEA	101	3.0	7.5 ml	54.0
DMF			60 ml	degassed with argon

The 4-(2,2-Dibromo-vinyl)-benzoic acid methyl ester (2) was made by the method of Wang Shen and Le Wang in J.Org.Chem. 1999, 64, 8873-8879.

**[0251]** A solution of 4-(2,2-dibromo-vinyl)-benzoic acid methyl ester (2) (5.76g, 18.0mmol), ethynyl-benzene (2.57g, 25.2mmol), Pd<sub>2</sub>dba<sub>3</sub> (164mg, 0.18mmol), tris(4-methoxyphenyl) phosphine (TMPP) (253mg, 0.72mmol) were dissolved in argon sparged (5 min.) DMF (60ml). The reaction was sparged with argon for 1 min. TEA (7.5ml, 54.0mmol) was added to the stirred reaction mixture that was then heated under argon at 85 °C for 3.5 hours. The reaction was found complete by LCMS. The reaction was cooled to rt and diluted with EtOAc/hexane (1:1) (300ml). The organic phase was washed with 1M HCl (2x50ml), 1M NaOH (3x50ml), water (2x50ml), sat. brine (50ml), dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to obtain 5.25g of crude product as an oil. The oil was treated with approximately 20 ml of a solution of 20% EtOAc/hexane that was heated to dissolve the residue. The walls of the flask were washed with the 20% EtOAc/hexane solution (5ml) that upon cooling gave 1.45 g of pure product (31% yield) as a white solid. The balance of the crude reaction product was purified by flash chromatography using EtOAc (8%)/hexane as eluant. The pure fractions were evaporated and dried *in vacuo* to give addition product typically 25-30% addition yield.

**[0252]** 4-(4-Phenyl-buta-1,3-dienyl)-benzoic acid methyl ester (4) was made according to the method of Wang Shen and Sheela A. Thomas in Org.Lett. 2000, 2(18), 2857-2860.

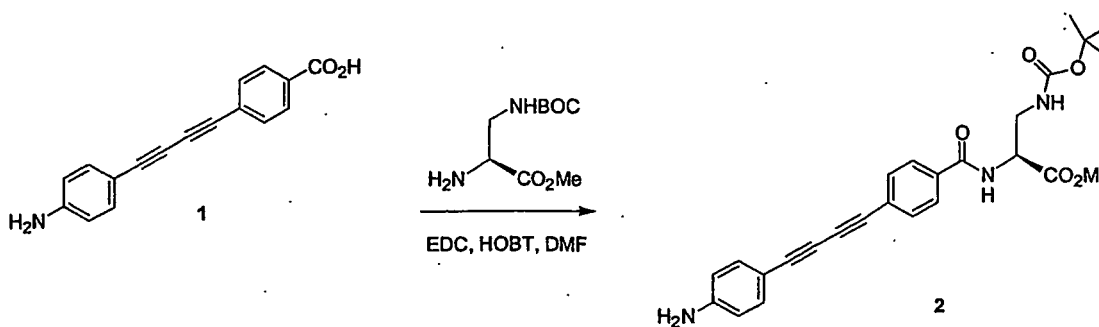
**Preparation of 4-(4-Phenyl-buta-1,3-diynyl)-benzoic acid (5)**

**[0253]** A 3M aq. solution of NaOH (20ml) was added to a stirred solution of methyl ester 4 (1.45g, 5.6mmol) in MeOH (100ml) at rt. The reaction solution was heated to reflux for 45 min. until the reaction turned clear. All of the starting material was gone by TLC and HPLC. The reaction was cooled to rt and some MeOH (~50ml) was removed by evaporation under reduced pressure. Water (100ml) was added to the mixture. Conc. HCl was added dropwise to the stirred solution until acidic by pH paper (pH2). The white precipitate that formed was collected by suction filtration. The solid was washed with water (3x20ml) and hexane (2x20ml) to give after drying 1.35 g of product acid 5 in 99% yield.

**[0254]** Subsequent conversion of compound 5 to compound 7 was performed according to the method described in Example 12 for the synthesis of *N*-(2-Hydroxy-1-hydroxycarbamoyl-propyl)-4-phenylethynyl-benzamide (compound 5). LCMS MH+ 363.13.

**Example B: Synthesis of N-[(1S)-1-(aminomethyl)-2-(hydroxyamino)-2-oxoethyl]-4-[4-(4-aminophenyl)buta-1,3-diynyl]benzamide**

Preparation of 2-{4-[4-(4-Amino-phenyl)-buta-1,3-diynyl]-benzoylamino}-3-tert-butoxycarbonylamino-propionic acid methyl ester (2).

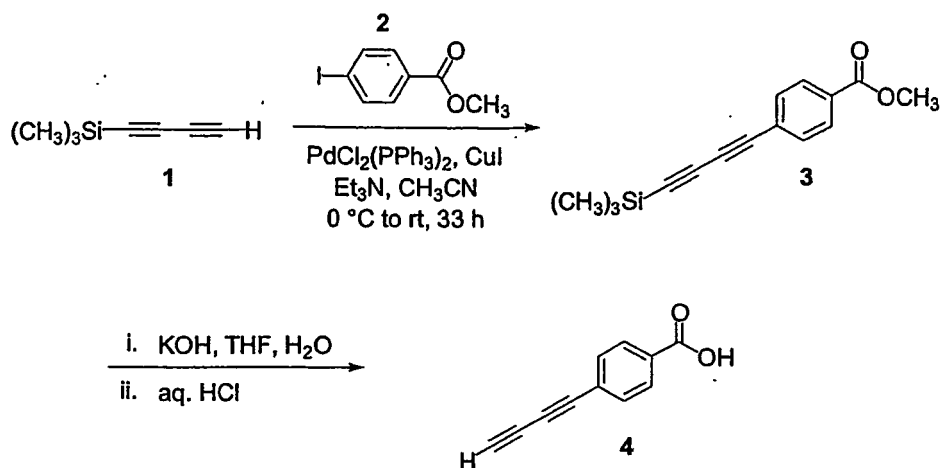
**[0255]**

Reagent	MW	EQ	g/ml	mmol
H-DAP(Boc)-OMe	254	1.05	5.12 g	20.1
1,3-diynyl benzoic acid (1)	261.3	1.0	5.0 g	19.1
HOBT	135.1	1.05	2.72 g	20.1
EDC	191.71	1.05	3.85 g	20.1
DIEA	129.25	3.0	10.5 ml	60.3
DMF			80 ml	

**[0256]** DIEA (10.5ml, 60.3mmol) was added to a stirred solution of 4-[4-(4-Amino phenyl)-buta-1,3-diynyl]-benzoic acid (1) (5.0g, 19.1mmol), HOBT (2.72g, 20.1mmol), EDC (3.85g, 20.1mmol) in DMF (80ml). After 2 min., the H-DAP (Boc)-OMe was added in one portion. After 12 hours at rt, the reaction was found complete by LCMS. The reaction was diluted with EtOAc/hexane (4:1) (500ml). The organic phase was washed with 1N NaOH (2x80ml), water (2x80ml), sat. brine (80ml), dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product. The residue was filtered through a filter plug of silica eluting with EtOAc/hexane (4:1). The fractions with product were evaporated to give 8.02 g of product in 91% yield.

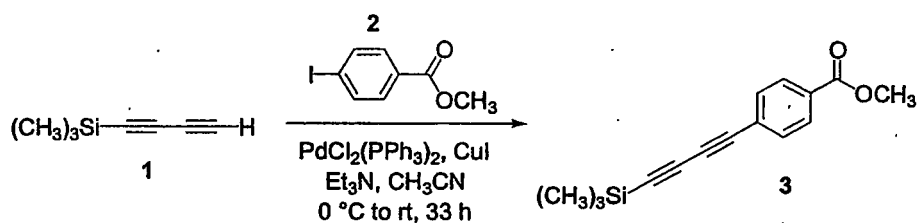
Subsequent conversion of compound 2 to the final hydroxamic acid (for example, Example 892) was performed according to the method described in Example 12 for the synthesis of *N*-(2-Hydroxy-1-hydroxycarbamoyl-propyl)-4-phenylethynyl-benzamide (compound 5).

**Synthesis of 4-(Buta-1,3-diynyl)-benzoic Acid (4) for making 1,3-diynyl analogues (such as Example 20 below)****[0257]**



Preparation of 4-(4-trimethylsilyl-buta-1,3-diynyl)-benzoic acid methyl ester (3).

[0258]

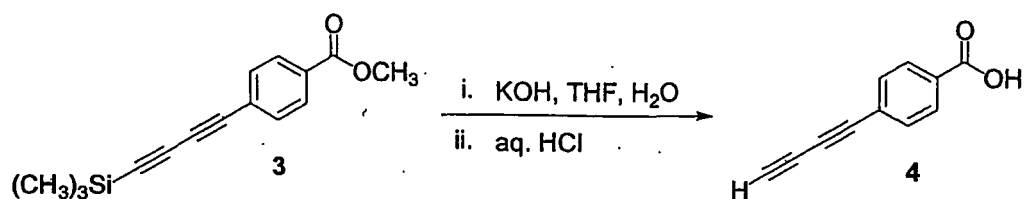


Reagent	MW	Eq.	g/ml	mmol
Methyl 4-iodobenzoate (2)	262.04	1.0	4.510 g	17.2
Trimethylsilylbutadiyne (1)	122.24	2.5	5.240 g	42.8
$\text{PdCl}_2(\text{PPh}_3)_2$	701.89	0.04	0.483 g	0.690
$\text{CuI}$	190.44	0.08	0.262 g	1.37
$\text{Et}_3\text{N}$	101.19	3.0	7.2 mL	52.0
$\text{CH}_3\text{CN}$			50 mL	

[0259] A solution of methyl 4-iodobenzoate 2 (4.510 g, 17.2 mmol),  $\text{PdCl}_2(\text{PPh}_3)_2$  (483 mg, 0.690 mmol), and  $\text{CuI}$  (262 mg, 1.37 mmol) in  $\text{CH}_3\text{CN}$  (50 mL) was cooled to  $0^\circ\text{C}$  under  $\text{N}_2$  atmosphere in the absence of light. Triethylamine (7.2 mL, 52.0 mmol) was added, followed by trimethylsilyl-1,3-butadiyne 1 (5.240 g, 42.8 mmol) and the reaction stirred 3 h at  $0^\circ\text{C}$  and 30 h at ambient temperature. Removal of solvent by rotary evaporation afforded a crude black residue that was purified by silica gel chromatography (95:5 hexanes/ $\text{EtOAc}$ ) to give 3.450 g (79% yield) of 4-(4-trimethylsilyl-buta-1,3-diynyl)-benzoic acid methyl ester 3 as a brown solid, mp =  $67-68^\circ\text{C}$ ,

Preparation of 4-(buta-1,3-diynyl)-benzoic acid (4).

[0260]



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Reagent	MW	Eq.	g/ml	mmol
Methyl ester (3)	252.34	1.0	3.420 g	13.5
KOH	56.11	4.9	3.700 g	65.9
H <sub>2</sub> O			10 mL	
THF			26 mL	

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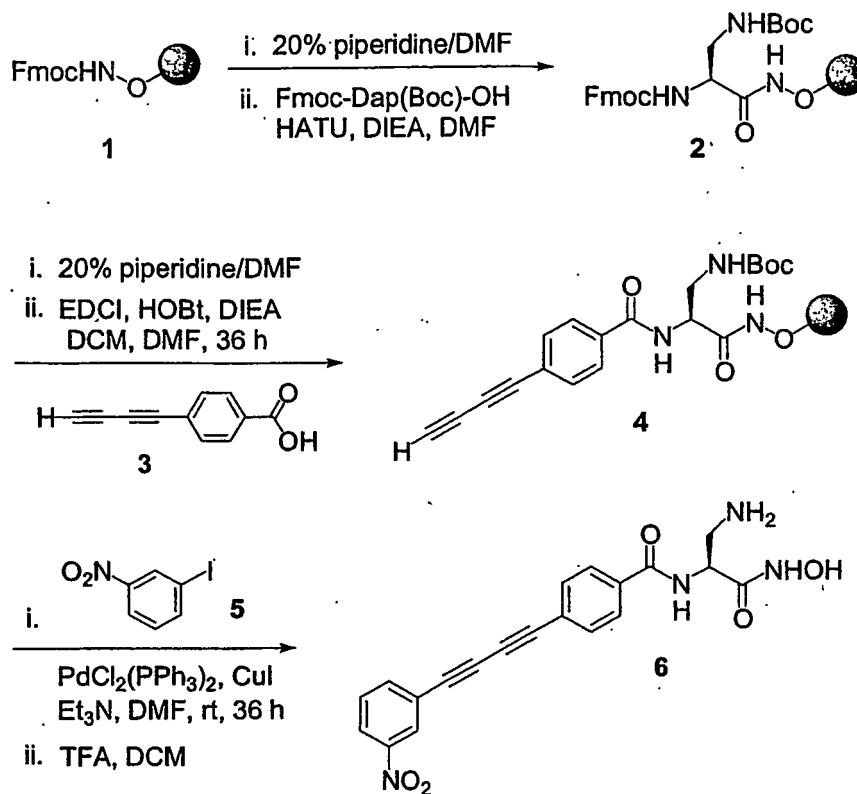
[0261] Potassium hydroxide (3.700 g, 65.9 mmol) was dissolved in H<sub>2</sub>O (10 mL) and added to a solution of 4-(4-trimethylsilylbuta-1,3-diynyl)-benzoic acid methyl ester **3** (3.420 g, 13.5 mmol) in THF (26 mL) in the absence of light. After stirring 16 h, the reaction was quenched with 1.0 M HCl (120 mL) and the resulting precipitate was filtered, washed with 1:1 hexanes/benzene (150 mL) and dried *in vacuo* to afford 2.100 g (91% yield, 98% pure) of 4-(buta-1,3-diynyl)-benzoic acid **4** as a brown solid, mp > 230 °C. Although diyne **4** was found to be unstable at room temperature it could be stored for several weeks at 0 °C with only small amounts of decomposition observed by TLC. R<sub>f</sub> = 0.2 (4:1 Hexanes/EtOAc); HPLC (300 nm, 28 min run) 16.0 min; LRMS (ES+) *m/z* 171.0 (C<sub>11</sub>H<sub>6</sub>O<sub>2</sub> + H requires 171.04).

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25 **Synthesis of a 3'-Nitrophenyl-Diacetylenic-Dap Hydroxamic Acid**

**Example 20: N-(1-(N-hydroxycarbamoyl)(1S)-2-aminoethyl){4-[4-(3-nitrophenyl)buta-1,3-diynyl]phenyl}carboxamide (6)**

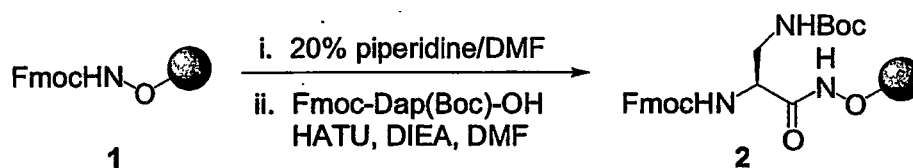
30 [0262]





## Preparation of Fmoc-Dap(Boc)-NHOH on hydroxylamine 2-chlorotrityl resin (2).

[0263]

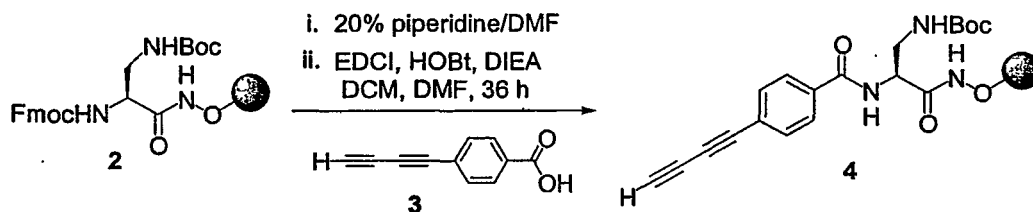


Reagent	MW	Eq.	g/mL	mmol
Hydroxylamine resin (1)	0.77 mmol/g	1.0	3.288 g	2.53
Fmoc-Dap(Boc)-OH	426.47	3.0	3.175 g	7.44
HATU	380.25	3.0	2.829 g	7.44
DIEA	129.25	10.0	4.3 mL	24.7
DMF			35 mL	

[0264] A suspension of N-Fmoc-hydroxylamine 2-chlorotrityl resin (3.288 g, 2.53 mmol, 0.77 mmol/g, Novabiochem) in DCM (40 mL) was shaken for 2 h and drained. The resin was treated with 20% piperidine in DMF (40 mL) for 1 hour, washed with DMF (2 × 40 mL), treated a second time with 20% piperidine in DMF (40 mL), washed with DMF (3 × 40 mL) and DCM (3 × 40 mL) and drained completely. In a separate flask, Fmoc-Dap(Boc)-OH (3.175 g, 7.44 mmol), HATU (2.829 g, 7.44 mmol) and DIEA (4.3 mL, 24.7 mmol) were dissolved in DMF (35 mL), stirred three minutes and added to the resin. After shaking for 48 h, the mixture was drained, washed with DMF (4 × 40 mL) and DCM (4 × 40 mL) and dried *in vacuo* to give 3.530 g of a yellow resin.

## Preparation of (S)-N-(2-N-Fmoc-amino-1-hydroxycarbamoyl-ethyl)-4-buta-1,3-diynyl-benzamide on hydroxylamine 2-chlorotrityl resin (4).

[0265]



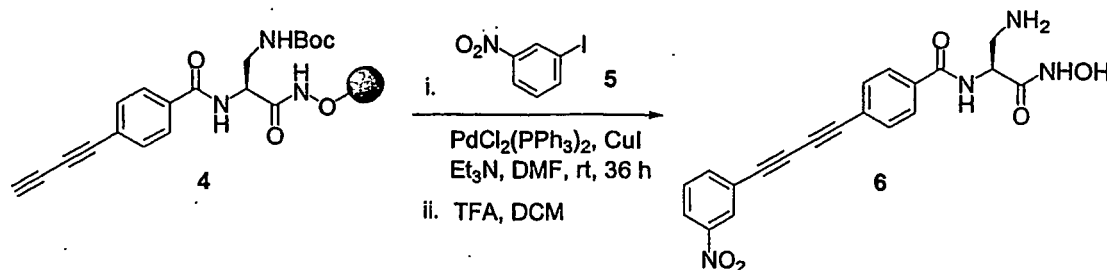
Reagent	MW	Eq.	g/mL	mmol
Fmoc-Dap(Boc)/resin (2)	0.71 mmol/g	1.0	3.530 g	2.53
Butadiynyl benzoic acid (3)	170.16	2.5	1.076 g	6.32
EDCI	191.71	3.0	1.457 g	7.60
HOBT	135.13	3.0	1.048 g	7.75
DIEA	129.25	5.0	2.2 mL	12.6
DCM			25 mL	
DMF			5 mL	

[0266] The resin 2 (3.530 g, 2.53 mmol, 0.71 mmol/g) was swelled in DCM (40 mL) for 2 h and drained. The resin was treated with 20% piperidine in DMF (40 mL) for 1 hour, washed with DMF (4 × 40 mL) and DCM (4 × 40 mL) and drained completely. In a separate flask, 4-buta-1,3-diynyl-benzoic acid 3 (1.076 g, 6.32 mmol), EDCI (1.457 g, 7.60 mmol), HOBT (1.048 g, 7.75 mmol) and DIEA (2.2 mL, 12.6 mmol) were dissolved in DCM (25 mL) and DMF (5 mL), stirred 45 min and added to the resin. After shaking for 48 h, the mixture was drained, washed with DMF (4 × 40 mL)

and DCM (4 × 40 mL) and dried *in vacuo* to give 3.35 g of a pale brown resin.

**Preparation of (S)-N-(2-amino-1-hydroxycarbamoyl-ethyl)-4-[4-(3-nitro-phenyl)-buta-1,3-diynyl]-benzamide (6).**

[0267]



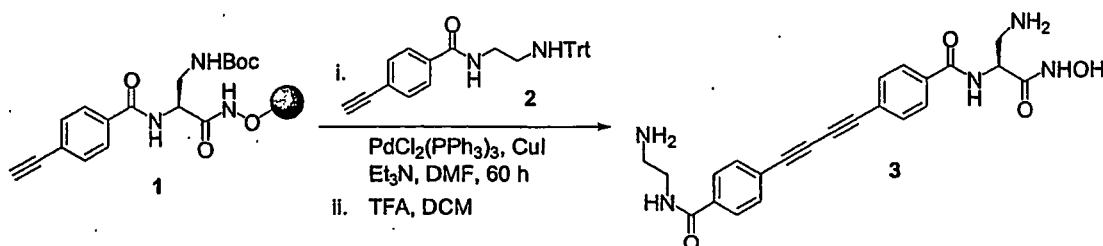
Reagent	MW	Eq.	g/mL	mmol
Diacetylene on resin (4)	0.77 mmol/g	1.0	176 mg	0.135
1-Iodo-3-nitrobenzene (5)	249.01	3.5	118 mg	0.474
PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	701.89	0.07	6.0 mg	0.009
CuI	190.44	0.38	10.0 mg	0.052
Et <sub>3</sub> N	101.19	10.6	200 μL	1.43
DMF			3.0 mL	

[0268] Resin 4 (176 mg, 0.135 mmol) was swelled in DCM (3 mL) for 1 h and drained. A solution of 1-iodo-3-nitrobenzene 5 (118 mg, 0.474 mmol) and Et<sub>3</sub>N (200 μL, 1.43 mmol) in DMF (3.0 mL) was purged with a stream of N<sub>2</sub> bubbles for two minutes and added to the resin. After mixing for 5 min, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (6.0 mg, 0.009 mmol) and CuI (10.0 mg, 0.052 mmol) were added and the mixture shaken for 36 h. The resin was drained, washed with DMF (4 × 3 mL), DCM (4 × 3 mL) and cleaved with 10% TFA/DCM (2 mL) for 20 min. The solution was collected and the resin was rinsed with additional 10% TFA/DCM (2 mL). The cleavage fractions were combined, treated with neat TFA (4.0 mL), stirred for 1 h at rt and concentrated by rotary evaporation to give a crude brown residue. Purification by RP-HPLC (C<sub>18</sub> column, CH<sub>3</sub>CN gradient 5-65%, 0.1% TFA, UV analysis 300 nm, 30 min) and lyophilization of the collected fractions afforded 12.0 mg (22%) of 470 as a white solid. LRMS (ES+) *m/z* 392.9 (C<sub>20</sub>H<sub>16</sub>N<sub>4</sub>O<sub>5</sub> + H requires 393.11); RP-HPLC (300 nm, 30 min run) 14.9 min.

**Synthesis of 4'-Benzamide Diacetylene Dap Hydroxamic Acid**

**Example 21: N-((2S)-amino-1-hydroxycarbamoyl-ethyl)-4-[4-[4-(2-amino-ethylcarbamoyl)-phenyl]-buta-1,3-diynyl]-benzamide (3)**

[0269]



**Preparation of N-((2S)-amino-1-hydroxycarbamoyl-ethyl)-4-{4-[4-(2-amino-ethylcarbamoyl)-phenyl]-buta-1,3-diynyl}-benzamide (3)**

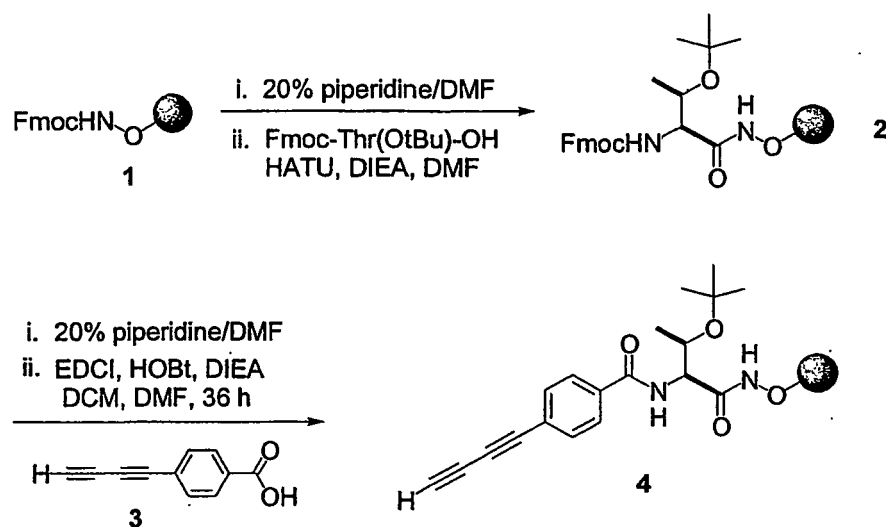
[0270]

Reagent	MW	Eq.	g/mL	mmol
Alkyne on resin (1)	0.77 mmol/g	1.0	145 mg	0.111
4-Ethynylbenzamide (2)	430.54	2.6	124 mg	0.288
PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	701.89	0.3	21 mg	0.030
CuI	190.44	1.0	22 mg	0.110
Et <sub>3</sub> N	101.19	6.5	100 $\mu$ L	0.72
DMF			2.0 mL	

[0271] Resin 1 (145 mg, 0.111 mmol) was swelled in DCM (2 mL) for 1 h and drained. A solution of 4-ethynylbenzamide 2 (124 mg, 0.288 mmol) and Et<sub>3</sub>N (100  $\mu$ L, 0.72 mmol) in DMF (2.0 mL) was added and the resin agitated for 5 min. A mixture of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (21 mg, 0.030 mmol) and CuI (22 mg, 0.110 mmol) was added and the resin was agitated for 60 h. The resin was drained, washed with DMF (3  $\times$  2 mL), DCM (3  $\times$  2 mL) and cleaved with 10% TFA/DCM (1.5 mL) for 20 min. The solution was collected and the resin was rinsed with additional 10% TFA/DCM (1.0 mL). The cleavage fractions were combined, treated with neat TFA (2.0 mL), stirred for 1 h at rt and concentrated by rotary evaporation to give a crude brown residue. Purification by RP-HPLC (C<sub>18</sub> column, CH<sub>3</sub>CN gradient 5-55%, 0.1% TFA, UV analysis 300 nm, 26 min) and lyophilization of the collected fractions afforded 2.6 mg (5% yield) of N-((2S)-amino-1-hydroxycarbamoyl-ethyl)-4-{4-[4-(2-amino-ethylcarbamoyl)-phenyl]-buta-1,3-diynyl}-benzamide. LRMS (ES+) *m/z* 434.0 (C<sub>23</sub>H<sub>23</sub>N<sub>5</sub>O<sub>4</sub> + H requires 434.19); RP-HPLC (300 nm, 26 min run) 15.3 min.

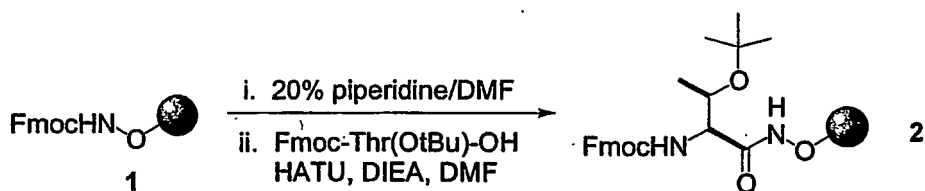
**Synthesis of N-[4-Butadiynyl-benzoyl]-Thr(tBu) on Resin (Continued to make Examples 22 and 23)**

[0272]



**Preparation of (2S, 3R)-2-N-Fmoc-amino-3-tert-butoxy-N-hydroxy-butryamide on hydroxylamine 2-chlorotriptyl resin (2).**

[0273]



Reagent	MW	Eq.	g/mL	mmol
Hydroxylamine resin (1)	0.77 mmol/g	1.0	3.188 g	2.45
Fmoc-Thr(tBu)-OH	397.50	3.0	2.927 g	7.36
HATU	380.25	3.0	2.798 g	7.36
DIEA	129.25	10.0	4.3 mL	24.6
DMF			40 mL	

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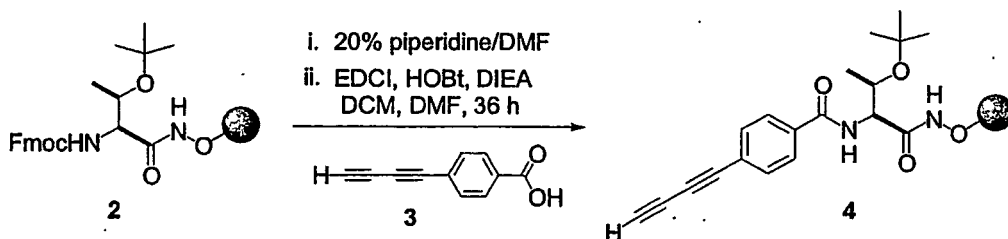
[0274] A suspension of N-Fmoc-hydroxylamine 2-chlorotrityl resin (3.188 g, 2.45 mmol, 0.77 mmol/g, Novabiochem) in DCM (40 mL) was shaken for 2 h and drained. The resin was treated with 20% piperidine in DMF (40 mL) for 1 hour, washed with DMF (2 × 40 mL), treated a second time with 20% piperidine in DMF (40 mL), washed with DMF (3 × 40 mL) and DCM (3 × 40 mL) and drained completely. In a separate flask, Fmoc-Thr(tBu)-OH (2.927 g, 7.36 mmol), HATU (2.798 g, 7.36 mmol) and DIEA (4.3 mL, 24.6 mmol) were dissolved in DMF (40 mL), stirred three minutes and added to the resin. After shaking for 24 h, the mixture was drained, washed with DMF (4 × 40 mL) and DCM (4 × 40 mL) and dried *in vacuo* to give 3.500 g of a yellow resin.

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**Preparation of 4-buta-1,3-diynyl-N-(2-tert-butoxy-1-hydroxycarbamoyl-propyl)-benzamide on hydroxylamine 2-chlorotrityl resin (4).**

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[0275]



Reagent	MW	Eq.	g/mL	mmol
Fmoc-threonine/resin (2)	0.77 mmol/g	1.0	2.030 g	1.56
Butadiynyl benzoic acid (3)	170.16	2.3	0.617 g	3.63
EDCI	191.71	2.8	0.834 g	4.35
HOBT	135.13	2.8	0.588 g	4.35
DIEA	129.25	3.7	1.0 mL	5.7
DCM			15 mL	
DMF			4 mL	

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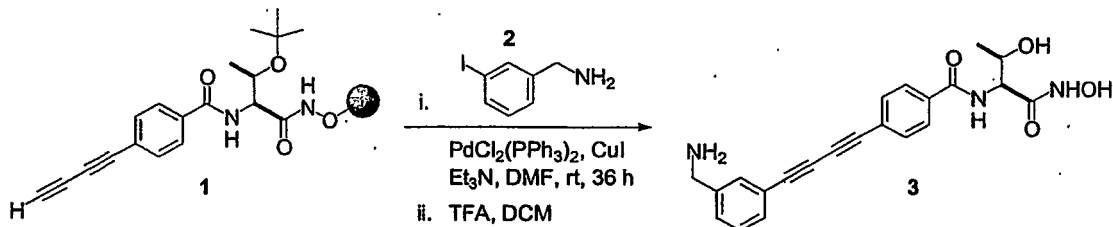
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[0276] The resin 2 (2.030 g, 1.56 mmol, 0.77 mmol/g) was swelled in DCM (20 mL) for 2 h and drained. The resin was treated with 20% piperidine in DMF (20 mL) for 1 hour, washed with DMF (4 × 20 mL) and DCM (4 × 20 mL) and drained completely. In a separate flask, 4-buta-1,3-diynyl benzoic acid 3 (0.617 g, 3.63 mmol), EDCI (0.834 g, 4.35 mmol), HOBT (0.588 g, 4.35 mmol) and DIEA (1.0 mL, 5.7 mmol) were dissolved in DCM (15 mL) and DMF (4 mL), stirred 45 min and added to the resin. After shaking for 36 h, the mixture was drained, washed with DMF (4 × 20 mL) and DCM (4 × 20 mL) and dried *in vacuo* to give 1.900 g of a pale brown resin.

## Synthesis of Diacetylenic Threonine Hydroxamic Acids

**Example 22: (2S,3R)-4-[4-(3-aminomethyl-phenyl)-buta-1,3-diynyl]-N-(2-hydroxy-1-hydroxycarbamoyl-propyl)-benzamide (3).**

[0277]



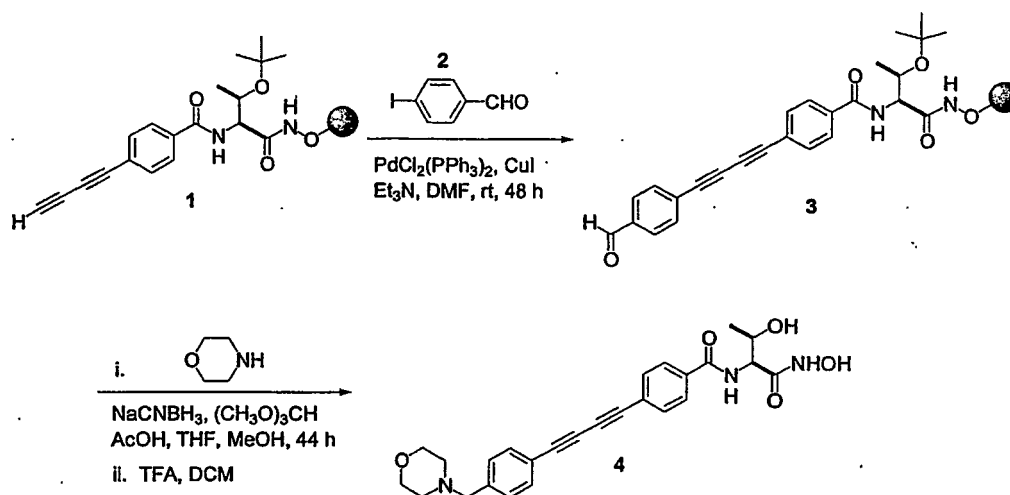
Reagent	MW	Eq.	g/mL	mmol
Diacetylene on resin (1)	0.77 mmol/g	1.0	100 mg	0.077
3-Iodobenzylamine HCl (2)	269.51	4.0	83.0 mg	0.308
$\text{PdCl}_2(\text{PPh}_3)_2$	701.89	0.2	11.0 mg	0.016
CuI	190.44	0.5	7.0 mg	0.037
$\text{Et}_3\text{N}$	101.19	23	250 $\mu\text{L}$	1.80
DMF			1.5 mL	

[0278] Resin **1** (obtained from previous synthesis) (100 mg, 0.077 mmol) was swelled in DCM (2 mL) for 1 h and drained. A solution of 3-iodobenzylamine hydrochloride **2** (83.0 mg, 0.308 mmol) and  $\text{Et}_3\text{N}$  (250  $\mu\text{L}$ , 1.80 mmol) in DMF (1.5 mL) was purged with a stream of  $\text{N}_2$  bubbles for two minutes and added to the resin. After mixing for 5 min,  $\text{PdCl}_2(\text{PPh}_3)_2$  (11.0 mg, 0.016 mmol) and CuI (7.0 mg, 0.037 mmol) were added and the mixture shaken for 36 h. The resin was drained, washed with DMF ( $4 \times 2$  mL), DCM ( $4 \times 2$  mL) and cleaved with 10% TFA/DCM (1.5 mL) for 20 min. The solution was collected and the resin was rinsed with additional 10% TFA/DCM (1.5 mL). The cleavage fractions were combined, treated with neat TFA (3.0 mL), stirred for 1 h at rt and concentrated by rotary evaporation to give a crude brown residue. Purification by RP-HPLC ( $\text{C}_{18}$  column,  $\text{CH}_3\text{CN}$  gradient 5-65%, 0.1% TFA, UV analysis 300 nm, 28 min) and lyophilization of the collected fractions afforded 4.3 mg (14%) of (2S,3R)-4-[4-(3-aminomethyl-phenyl)-buta-1,3-diynyl]-N-(2-hydroxy-1-hydroxycarbamoyl-propyl)-benzamide as a white solid. LRMS (ES+)  $m/z$  392.0 ( $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_4 + \text{H}$  requires 392.15); RP-HPLC (300 nm, 28 min run) 10.0 min.

## Synthesis of Diacetylenic Benzylamine Analogues

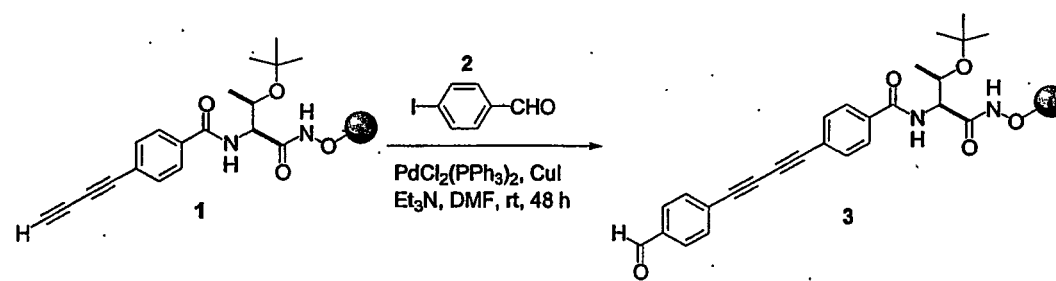
**Example 23: (1S, 2R)-N-2-hydroxy-1-hydroxycarbamoyl-propyl)-4-[4-(4-morpholin-4-ylmethyl-phenyl)-buta-1,3-diynyl]-benzamide (4)**

[0279]



Preparation of threonine diacetylenic benzaldehyde on resin (3).

[0280]

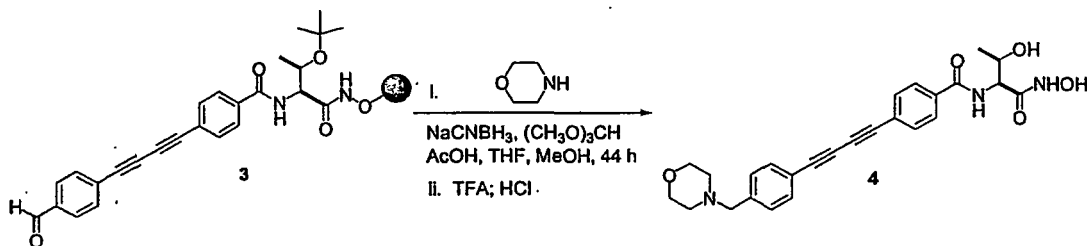


Reagent	MW	Eq.	g/mL	mmol
Diacetylene on resin (1)	0.77 mmol/g	1.0	1.00 g	0.770
4-Iodobenzaldehyde	232.00	4.0	715 mg	3.081
$\text{PdCl}_2(\text{PPh}_3)_2$	701.89	0.07	40.0 mg	0.057
CuI	190.44	0.13	19.0 mg	0.100
$\text{Et}_3\text{N}$	101.19	9.3	1.00 mL	7.17
DMF			20.0 mL	

[0281] Resin 1 (1.00 g, 0.77 mmol) was pre-swelled in DCM (25 mL) for 14 h and drained. A solution of 4-iodobenzaldehyde 2 (715 mg, 3.08 mmol) and  $\text{Et}_3\text{N}$  (1.00 mL, 7.17 mmol) in DMF (20 mL) was purged with  $\text{N}_2$  for two minutes and added to the resin. After mixing for 5 min,  $\text{PdCl}_2(\text{PPh}_3)_2$  (40.0 mg, 0.057 mmol) and CuI (19.0 mg, 0.100 mmol) were added and the reaction shaken for 48 h. The resin was drained, washed with DMF ( $4 \times 20$  mL), DCM ( $4 \times 20$  mL) and dried *in vacuo* to give 1.100 g of a dark yellow resin.

Preparation of (1S, 2R)-N-2-hydroxy-1-hydroxycarbamoyl-propyl)-4-[4-(4-morpholin-4-ylmethyl-phenyl)-buta-1,3-diynyl]-benzamide (4).

[0282]



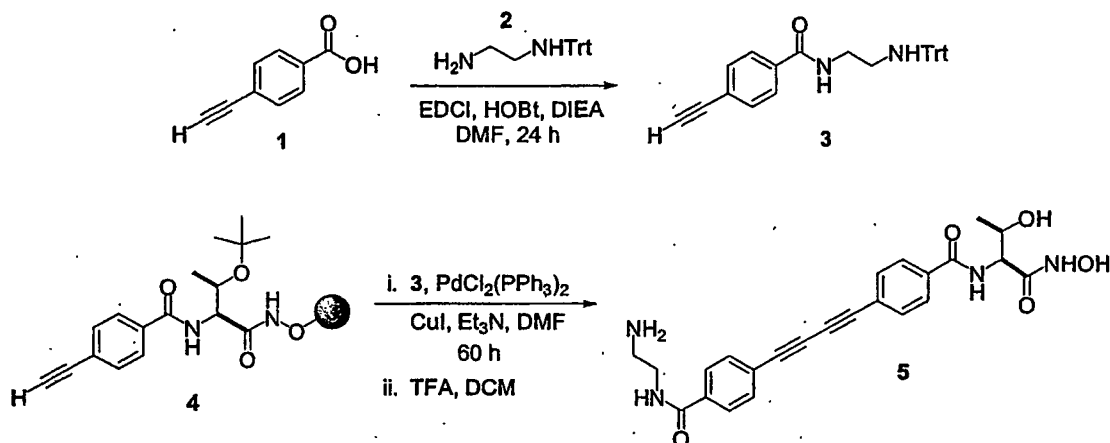
Reagent	MW	Eq.	mg/ $\mu$ l	mmol
Benzaldehyde on resin ( <b>3</b> )	0.77 mmol/g	1.0	188 mg	0.141
Morpholine	87.12	6.0	75 $\mu$ L	0.860
NaCNBH <sub>3</sub>	62.84	4.5	40 mg	0.637
Trimethyl orthoformate	106.12	6.5	100 $\mu$ L	0.914
Acetic acid	60.05	12.3	100 $\mu$ L	1.750
THF			3.0 mL	
MeOH			1.0 mL	

**[0283]** A solution of morpholine (75  $\mu$ L, 0.860 mmol) and trimethyl orthoformate (100  $\mu$ L, 0.914 mmol) in THF (3.0 mL) was added to a Teflon-lined screw-capped vial containing the resin-bound diacetylenic benzaldehyde **3**. The resin was agitated for 10 min, treated successively with acetic acid (100  $\mu$ L, 1.75 mmol) and a solution of NaCNBH<sub>3</sub> (40.0 mg, 0.637 mmol) in MeOH (1.0 mL) and shaken for 44 h. The resin was filtered, washed with DMF (3  $\times$  3 mL) and DCM (3  $\times$  3 mL) and drained. Cleavage from the resin was achieved by treatment with 10% TFA/DCM (2.0 mL) and shaking 20 min. The solution was collected and the resin was rinsed with additional 10% TFA/DCM (2.0 mL). The cleavage fractions were combined, treated with neat TFA (3.0 mL), stirred for 1 h at rt and concentrated by rotary evaporation to give a crude yellow residue. Purification by RP-HPLC (C<sub>18</sub> column, CH<sub>3</sub>CN gradient 5-35%, 0.1% TFA, UV analysis 300 nm, 18 min) and lyophilization of the collected fractions afforded 19.0 mg (29%) of **472** as a fluffy yellow solid. LRMS (ES<sup>+</sup>) *m/z* 462.0 (C<sub>26</sub>H<sub>27</sub>N<sub>3</sub>O<sub>5</sub> + H requires 462.10); HPLC (300 nm, 18 min run) 10.3 min.

#### Synthesis of 4'-Benzamide Diacetylene Threonine Hydroxamic Acid

**Example 24: (1S,2R)-N-(2-hydroxy-1-hydroxycarbamoyl-propyl)-4-{4-[4-(2-amino-ethylcarbamoyl)-phenyl]-buta-1,3-diynyl}-benzamide (**5**)**

**[0284]**



**Preparation of N-(2-trityl-amino-ethyl)-4-ethynyl-benzamide (3).****[0285]**

	Reagent	MW	Eq.	g/mL	mmol
5	4-Ethynylbenzoic acid (1)	146.14	1.0	0.292 g	2.00
	N-Trityl ethylenediamine	302.41	1.3	0.810 g	2.67
	EDCI	191.71	1.0	0.382 g	2.00
10	HOBt	135.13	3.0	0.270 g	2.00
	DIEA	129.25	4.0	1.40 mL	8.00
	DMF			10.0 mL	

**[0286]** To a solution of 4-ethynylbenzoic acid 1 (292 mg, 2.00 mmol), EDCI (382 mg, 2.00 mmol), and HOBt (270 mg, 2.00 mmol) in DMF (10 mL) was added N-trityl ethylenediamine 2 (810 mg, 2.67 mmol) and DIEA (1.4 mL, 8.0 mmol). The reaction mixture was stirred 24 h, diluted with EtOAc (200 mL), washed with 0.5 M HCl (60 mL), saturated NaHCO<sub>3</sub> (2 × 60 mL), H<sub>2</sub>O (4 × 60 mL), dried over MgSO<sub>4</sub> and concentrated to give 836 mg (97% yield) of N-(2-trityl-amino-ethyl)-4-ethynyl-benzamide 3 as a white solid, mp 50-51 °C. R<sub>f</sub> = 0.40 (1:1 Hexanes/EtOAc).

**Preparation of (1S,2R)-N-(2-hydroxy-1-hydroxycarbamoyl-propyl)-4-{4-[4-(2-amino-ethylcarbamoyl)-phenyl]-buta-1,3-diynyl}-benzamide (5).**

**[0287]**

	Reagent	MW	Eq.	g/mL	mmol
25	Alkyne on resin (4)	0.77 mmol/g	1.00	150 mg	0.116
	4-Ethynylbenzamide (3)	430.54	3.00	151 mg	0.350
	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	701.89	0.25	21 mg	0.030
30	CuI	190.44	1.25	28 mg	0.147
	Et <sub>3</sub> N	101.19	9.50	150 μL	1.10
	DMF			2.0 mL	

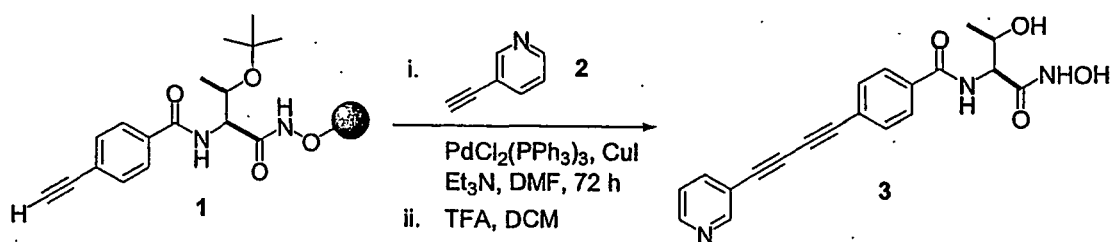
**[0288]** Resin 4 (150 mg, 0.116 mmol) was swelled in DCM (2 mL) for 1 h and drained. A solution of 4-ethynylbenzamide 3 (151 mg, 0.350 mmol) and Et<sub>3</sub>N (150 μL, 1.10 mmol) in DMF (2.0 mL) was added and the resin agitated for 5 min. A mixture of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (21 mg, 0.030 mmol) and CuI (28 mg, 0.147 mmol) was added and the resin was agitated for 60 h. The resin was drained, washed with DMF (3 × 2 mL), DCM (3 × 2 mL) and cleaved with 10% TFA/DCM (1.5 mL) for 20 min. The solution was collected and the resin was rinsed with additional 10% TFA/DCM (1.0 mL). The cleavage fractions were combined, treated with neat TFA (2.0 mL), stirred for 1 h at rt and concentrated by rotary evaporation to give a crude brown residue. Purification by RP-HPLC (C<sub>18</sub> column, CH<sub>3</sub>CN gradient 5-65%, 0.1% TFA, UV analysis 300 nm, 26 min) and lyophilization of the collected fractions afforded 2.0 mg (4% yield) of (1S,2R)-N-(2-hydroxy-1-hydroxycarbamoyl-propyl)-4-{4-[4-(2-amino-ethylcarbamoyl)-phenyl]-buta-1,3-diynyl}-benzamide. LRMS (ES+) m/z 449.1 (C<sub>24</sub>H<sub>24</sub>N<sub>4</sub>O<sub>5</sub> + H requires 449.18); RP-HPLC (300 nm, 26 min run) 17.0 min.

**Synthesis of 3'-Pyridine Diacetylene Threonine Hydroxamic Acid**

**Example 25: N-((2R)-hydroxy-(1S)-hydroxycarbamoyl-propyl)-4-(4-pyridin-3-yl-but-1,3-diynyl)-benzamide (3)**

**[0289]**





**Preparation of N-((2R)-hydroxy-(1S)-hydroxycarbamoyl-propyl)-4-(4-pyridin-3-yl-buta-1,3-diynyl)-benzamide (3).**

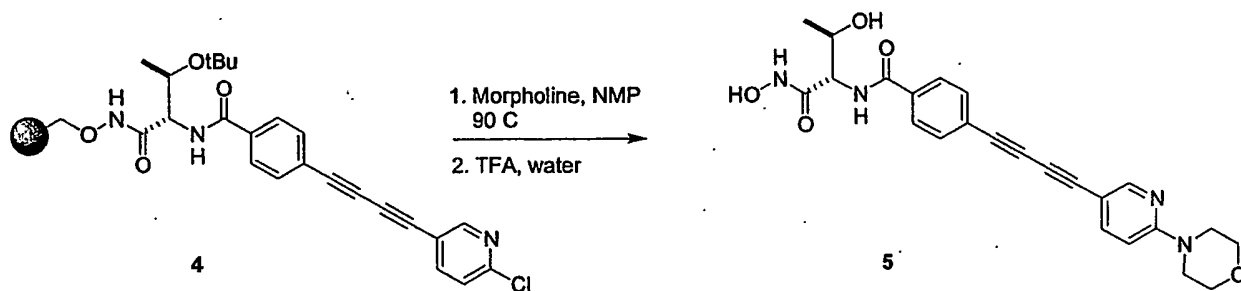
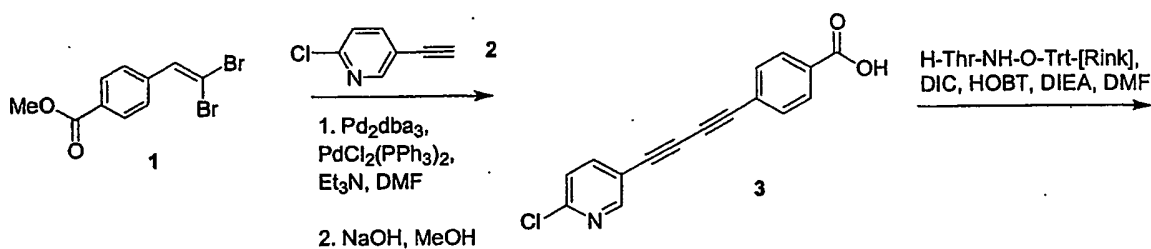
[0290]

Reagent	MW	Eq.	g/mL	mmol
Alkyne on resin (1)	0.77 mmol/g	1.0	142 mg	0.109
3-Ethynylpyridine (2)	103.12	3.4	38 mg	0.368
$\text{PdCl}_2(\text{PPh}_3)_2$	701.89	0.3	22 mg	0.031
CuI	190.44	1.2	25 mg	0.131
$\text{Et}_3\text{N}$	101.19	13	200 $\mu\text{L}$	1.40
DMF			2.0 mL	

[0291] Resin 1 (142 mg, 0.109 mmol) was swelled in DCM (2 mL) for 1 h and drained. A solution of 3-ethynylpyridine 2 (38 mg, 0.368 mmol) and  $\text{Et}_3\text{N}$  (200  $\mu\text{L}$ , 1.4 mmol) in DMF (2 mL) was added and the resin agitated for 5 min. A mixture of  $\text{PdCl}_2(\text{PPh}_3)_2$  (22 mg, 0.031 mmol) and CuI (25 mg, 0.131 mmol) was added and the resin was agitated for 72 h. The resin was drained, washed with DMF ( $3 \times 2$  mL), DCM ( $3 \times 2$  mL) and cleaved with 10% TFA/DCM (1.5 mL) for 20 min. The solution was collected and the resin was rinsed with additional 10% TFA/DCM (1.0 mL). The cleavage fractions were combined, treated with neat TFA (2.0 mL), stirred for 1 h at rt and concentrated by rotary evaporation to give a crude brown residue. Purification by RP-HPLC ( $\text{C}_{18}$  column,  $\text{CH}_3\text{CN}$  gradient 5-65%, 0.1% TFA, UV analysis 300 nm, 24 min) and lyophilization of the collected fractions afforded 4.4 mg (11% yield) of N-((2R)-hydroxy-(1S)-hydroxycarbamoyl-propyl)-4-(4-pyridin-3-yl-buta-1,3-diynyl)-benzamide. LRMS (ES+)  $m/z$  364.0 ( $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_4 + \text{H}$  requires 364.13); RP-HPLC (300 nm, 24 min run) 11.2 min.

**Example 26: Synthesis of N-(1-(N-hydroxycarbamoyl)(1S,2R)-2-hydroxy propyl){4-[4-(6-morpholin-4-yl(3-pyridyl))buta-1,3-diynyl]phenyl} carboxamide (5)**

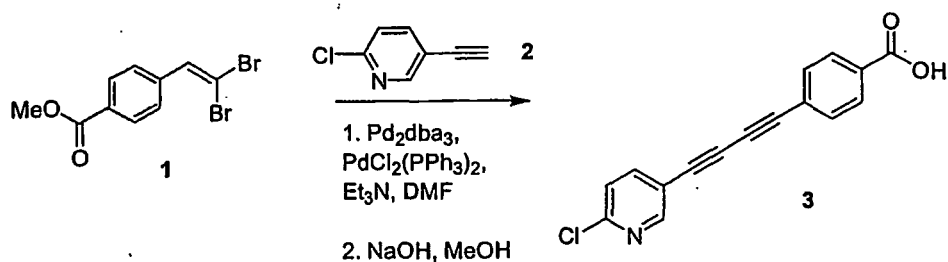
[0292]



Reagent	MW	EQ	g/ml	mmol
Dibromovinylbenzoic acid (1)	320	1.0	9.6 g	30.0
2-Chloro-5-ethynyl-pyridine	138	1.3	5.43 g	39.0
$\text{Pd}_2\text{dba}_3$	915	0.01	274 mg	0.3 (1% cat.)
TMPP	352	0.04	422 mg	1.2 (4%)
TEA	101	3.0	12.5 ml	90.0
DMF			90 ml	degassed with argon

#### Preparation of 4-[4-(6-Chloro-pyridin-3-yl)-buta-1,3-diynyl]-benzoic acid methyl ester.

[0293]



[0294] 4-[4-(6-Chloro-pyridin-3-yl)-buta-1,3-diynyl]-benzoic acid was made according to the method of Wang Shen and Sheela A. Thomas in Org.Lett. 2000, 2(18), 2857-2860.

[0295] A solution of 4-(2,2-dibromo-vinyl)-benzoic acid methyl ester (1) (9.6g, 30.0mmol), ethynylpyridine (2) (5.43g, 39.0mmol),  $\text{Pd}_2\text{dba}_3$  (274mg, 0.3mmol), tris(4-methoxyphenyl) phosphine (TMPP) (422mg, 1.2mmol) were dissolved in argon sparged (5 min.) DMF (60ml). The reaction was sparged with argon for 1 min. TEA (12.5ml, 90.0mmol) was added to the stirred reaction mixture that was then heated under argon at 85 °C for 3 hours. The reaction was found complete by LCMS. The reaction was cooled to rt and diluted with EtOAc/hexane (1:1) (500ml). The organic phase was washed with 1M NaOH (2x80ml), water (2x80ml), sat. brine (80ml), dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give crude product. The residue was filtered through a filter plug of silica eluting with EtOAc/hexane (1:1). The fractions with product were evaporated to give 9.06 g of product in good purity (~96% pure). The material

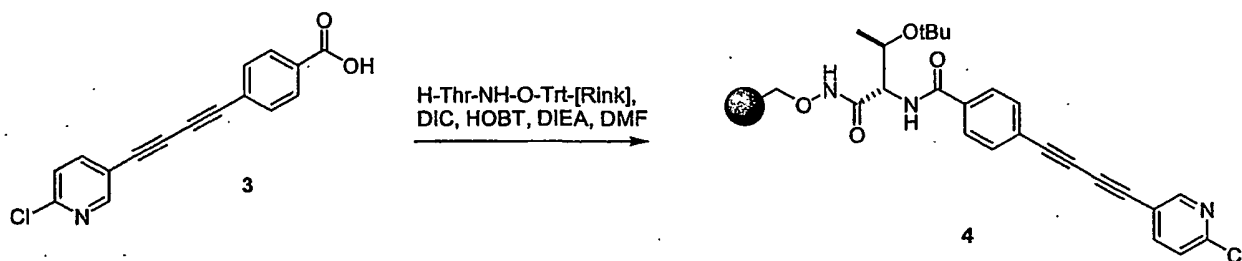
was taken on without further purification.

### Preparation of 4-[4-(6-Chloro-pyridin-3-yl)-buta-1,3-diynyl]-benzoic acid (3)

**[0296]** A 6M aq. solution of NaOH (15ml) was added to a stirred solution of 4-[4-(6-Chloro-pyridin-3-yl)-buta-1,3-diynyl]-benzoic acid methyl ester. (9.06g, 30mmol) in MeOH (350ml) at rt. The reaction solution was heated to reflux for 3 hours. The reaction stayed a mixture and did not turn clear. HPLC and LCMS indicated that the reaction was forming side products. The reaction was cooled to rt and some MeOH (~200ml) was removed by evaporation under reduced pressure. Water (400ml) was added to the mixture. Conc. HCl was added dropwise to the stirred solution until acidic by pH paper (pH2). The yellow precipitate that formed was collected by suction filtration. The solid was washed with water (3x20ml) and hexane (2x20ml) to give the crude product. HPLC indicated that there was approximately 40% product in the mixture. The crude reaction product was purified by flash chromatography using EtOAc (8-10%)/hexane as eluant. The pure fractions were evaporated and dried *in vacuo* to give 4.2 g of product **3** in 50% yield.

### Preparation of [4-[4-(6-chloro-pyridin-3-yl)-buta-1,3-diynyl]-benzoyl]-HN-Thr(OtBu)-hydroxamic acid trityl resin (4)

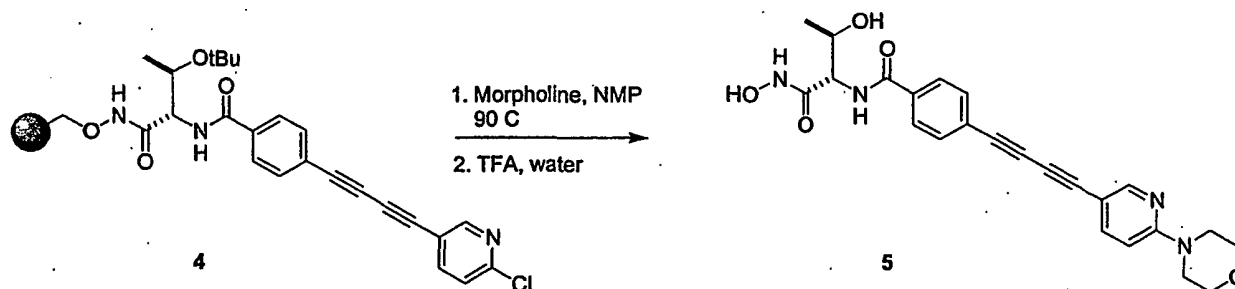
**[0297]**



**[0298]** 4-[4-(6-Chloro-pyridin-3-yl)-buta-1,3-diynyl]-benzoic acid (**3**) was coupled to a tert-butyl protected threonine pre-loaded on hydroxylamine 2-chlorotrityl resin following the same procedure as used for Example 26. The coupling employed DIC and HOBT. [N-Fmoc-hydroxylamine 2-chlorotrityl resin was purchased from Novabiochem cat.# 01-64-0165.]

### Preparation of N-(2-Hydroxy-1-hydroxycarbamoyl-propyl)-4-[4-(6-morpholin-4-yl-pyridin-3-yl)-buta-1,3-diynyl]-benzamide (5)

**[0299]**

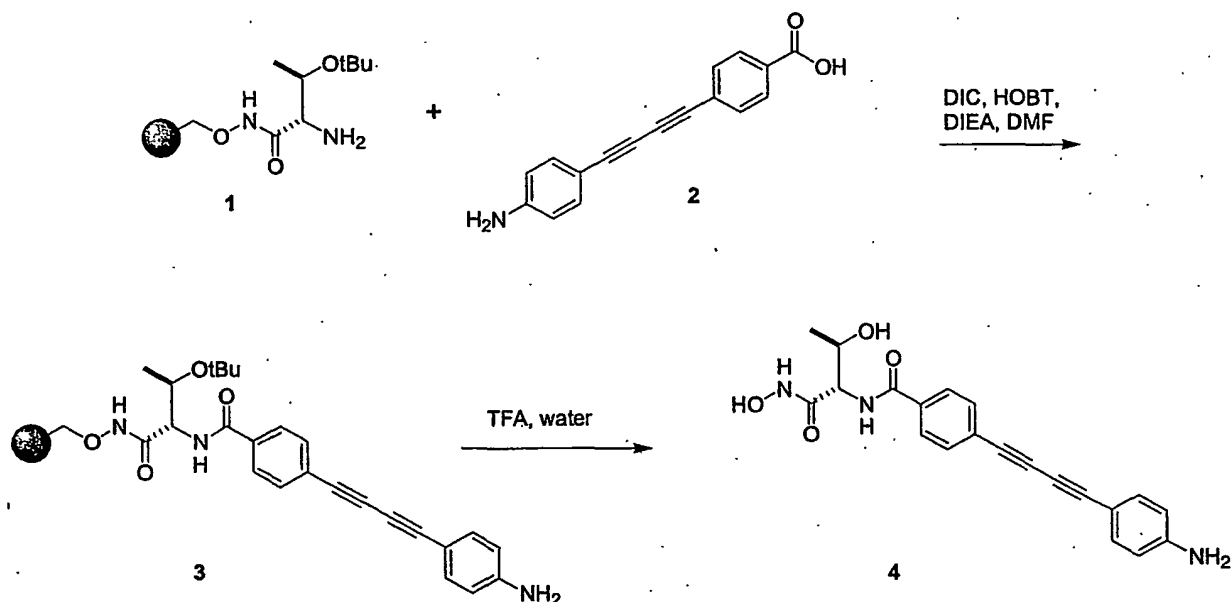


**[0300]** A solution of morpholine (300uL) in NMP (1ml) was added to a vial containing the 2-chloropyridine resin (**4**) (150mg, 0.12mmol). The reaction mixture was purged with argon and heated to 85-90 °C for 24 hours. The resin was drained and washed with DMF and DCM alternately several times. The product was cleaved from the resin through treatment with a TFA/water solution (80:20) (1.5ml) for 45 min. The resin was filtered and washed with fresh TFA/water solution (80:20) (0.5ml). The combined TFA and organic fractions were diluted with CH<sub>3</sub>CN/water (1:1) (10ml), water (2ml) and lyophilized. The crude product was purified by prep. HPLC. The crude product was dissolved in DMSO (1ml), passed through a Teflon syringe filter, and the clear filtrate was injected on a preparative HPLC. The purification used

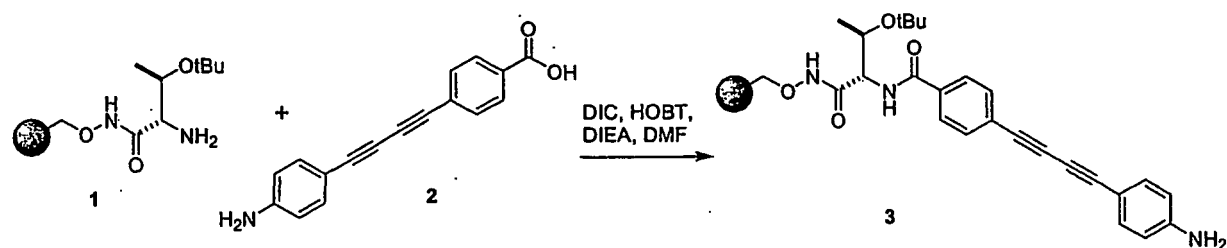
a 20x50 mm Ultro 120 C18 column running a 22 ml/min 2% gradient (AcCN/water, 0.1% TFA) for 16 min. The purified fractions were lyophilized to dryness to give 2.2 mg of pure product as the TFA salt (~32% yield).

**Example 27: Synthesis of 4-[4-(4-Amino-phenyl)-buta-1,3-diynyl]-N-(2-hydroxy-1-hydroxycarbamoyl-propyl)-benzamide (4)**

[0301]



**[0302]** Preparation of 2-[4-[4-(4-Amino-phenyl)-buta-1,3-diynyl]-benzoylamino]-3-tert-butoxycarbonyloxy-butyrilc hydroxamic acid trityl resin (3).



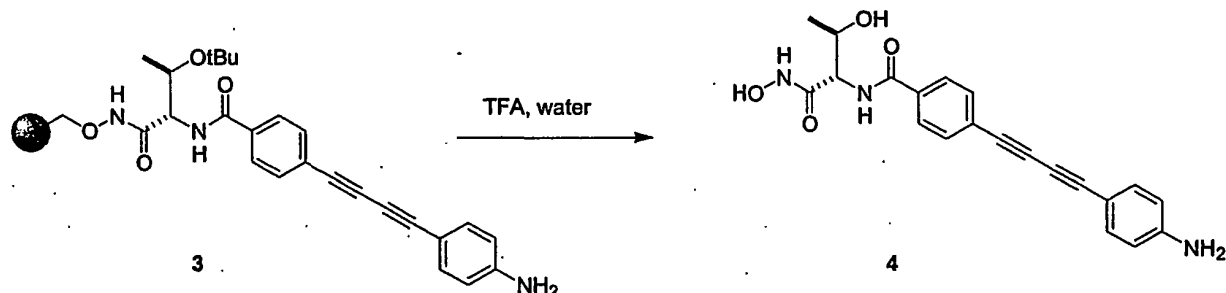
Reagent	MW	EQ	g/ml	mmol
H-Thr(Boc)-NHO-Trt Resin (1)		1.0	5.8 g	4.47
1,3-diynyl benzoic acid (2)	261.3	1.4	1.64 g	6.25
HOBT	135.1	1.4	0.85 g	6.25
DIC	126.2	1.4	0.98 ml	6.25
DIEA	129.25	3.5	2.7 ml	15.6
DMF			50 ml	

**[0303]** DIEA (2.7ml, 15.6mmol) was added to a stirred solution of 4-[4-(4-Amino-phenyl)-buta-1,3-diynyl]-benzoic acid (2) (1.64g, 6.3mmol), HOBT (0.85g, 6.3mmol), DIC (0.98ml, 6.3mmol) in DMF (50ml). After 2 min., the Thr hydroxylamine resin (5.8g, 4.5mmol) was added in one portion. [N-Fmoc-hydroxylamine 2-chlorotrityl resin was purchased from Novabiochem cat.# 01-64-0165.] After 12 hours at rt, the reaction was found complete by LCMS. The resin was drained and washed with DMF and DCM alternately 3 times each. The product on resin 3 was used as is in subsequent reactions

without further treatment.

**Preparation of 4-[4-(4-Amino-phenyl)-buta-1,3-diynyl]-N-(2-hydroxy-1-hydroxy carbamoyl-propyl)-benzamide (4)**

[0304]

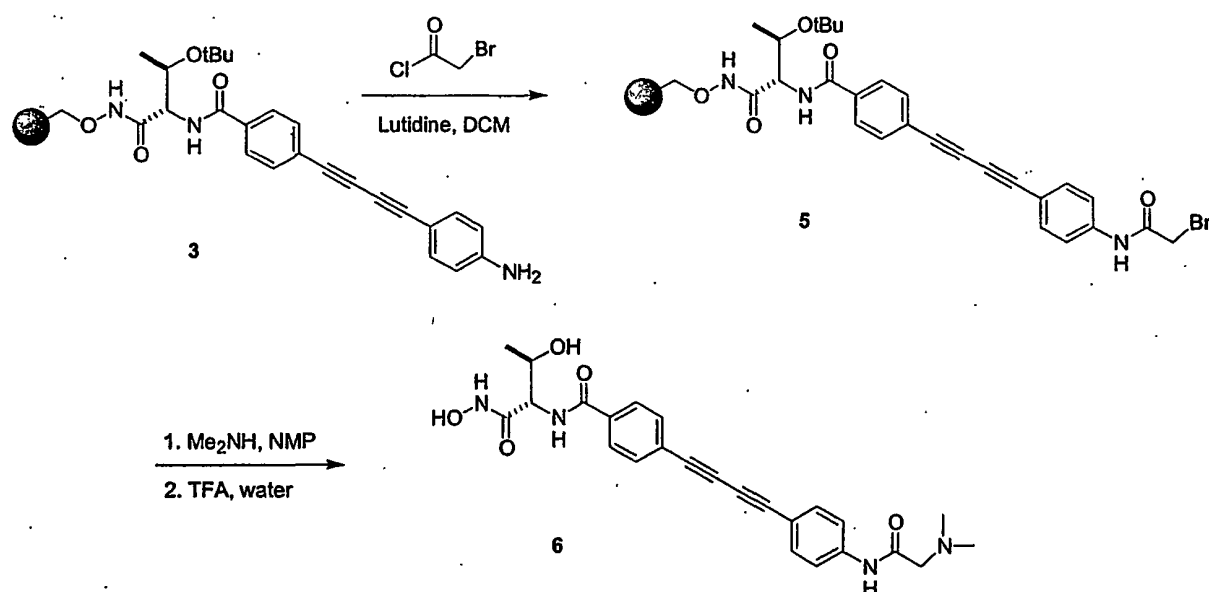


Reagent	MW	EQ	g/ml	mmol
1,3-diynyl benzoic Thr Resin (3)		1.0	120 mg	0.09
TFA/water (80:20)			1.5 ml	

**[0305]** The product (**4**) (120mg, 0.09mmol) was cleaved from the resin through treatment with a TFA/water solution (80:20) (1.5ml) for 45 min. The resin was filtered and washed with fresh TFA/water solution (80:20) (0.5ml). The combined TFA and organic fractions were diluted with CH<sub>3</sub>CN/water (1:1) (10ml), water (2ml) and lyophilized. The crude product was purified by prep. HPLC. The crude product was dissolved in DMSO (1ml), passed through a Teflon syringe filter, and the clear filtrate was injected on a preparative HPLC. The purification used a 20x50 mm Ultro 120 C18 column running a 22 ml/min 2% gradient (AcCN/water, 0.1% TFA) for 16 min. The purified fractions were lyophilized to dryness to give 2.2 mg of pure product as the TFA salt. The product (**4**) was lyophilized again from CH<sub>3</sub>CN/water with 10 equivalents of HCl to remove most of the TFA to yield 2 mg of product as the HCl salt (~53% yield).

**Example 28: Synthesis of 4-[4-[4-(2-Dimethylamino-acetyl-amino)-phenyl]-buta-1,3-diynyl]-N-(2-hydroxy-1-hydroxycarbamoyl-propyl)-benzamide (6) (Continued from compound 3 of Example 27 above)**

[0306]



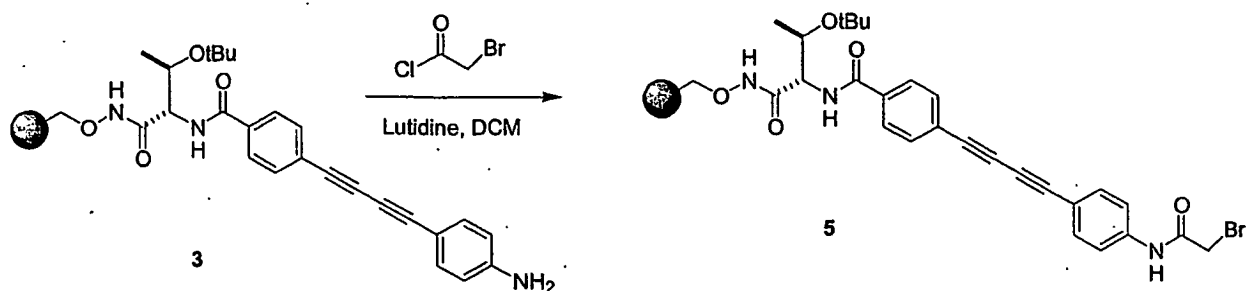
**Preparation of 2-(4-[4-(2-Bromo-acetyl-amino)-phenyl]-buta-1,3-diynyl)-benzoylamino)-3-tert-butoxycarbonyloxy-butyric acid hydroxamate trityl resin (5).**

[0307]

5

10

15



20

Reagent	MW	EQ	g/ml	mmol
Amino 1,3-diynyl benzoic Thr Trt Resin ( <b>3</b> )		1.0	0.75 g	0.578
Bromo-acetyl chloride	157.4	8.0	0.728 g	4.62
Lutidine	107	10.0	1.07 ml	9.24
DMF			6 ml	

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**[0308]** A solution of bromo-acetyl chloride (0.75g, 0.58mmol) in DCM (2ml) was added to a mixture of 2-(4-[4-(4-Amino-phenyl)-buta-1,3-diynyl]-benzoylamino)-3-tert-butoxycarbonyloxy-butyric acid hydroxamate Trt Resin (**3**) (0.75g, 0.58mmol), lutidine (1.1ml, 9.2mmol) and DCM (4ml) at rt with shaking. After shaking for 1.5 hours, the reaction was found complete by LCMS. The resin was drained and washed with DCM (2x10ml), DMF (3x10ml) and DCM (3x10ml) again. The resin was drained and dried in vacuo. The product on resin **5** was used as is in subsequent reactions without further treatment.

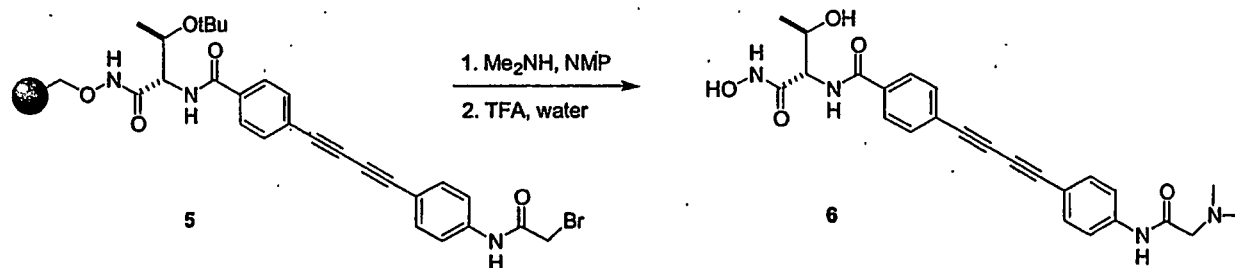
**Preparation of 4-[4-[4-(2-Dimethylamino-acetyl-amino)-phenyl]-buta-1,3-diynyl]-N-(2-hydroxy-1-hydroxycarbamoyl-propyl)-benzamide (6).**

[0309]

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Reagent	MW	EQ	g/ml	mmol
Bromo acetic Thr Trt Resin ( <b>5</b> )		1.0	125 mg	0.093
Dimethyl amine	45.08		0.2 ml	excess
NMP			1.2 ml	

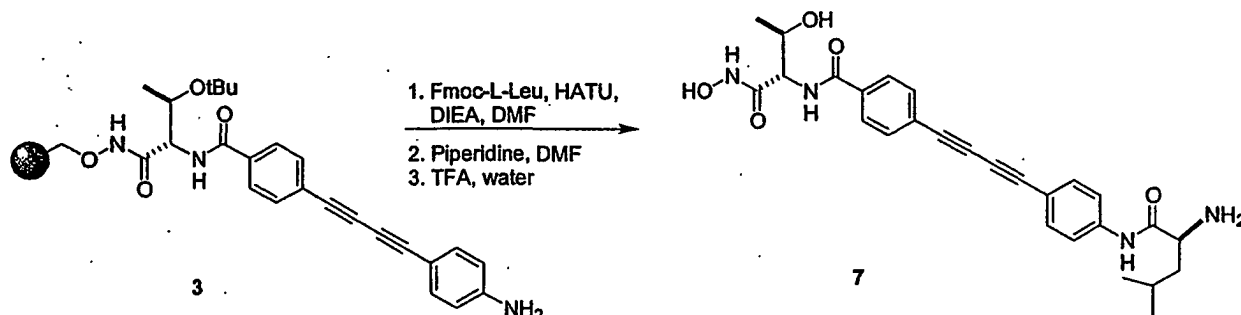
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**[0310]** A solution of dimethyl amine (0.2ml) in NMP (1.2ml) was added to bromo acetic Thr Trt Resin (**5**) (125 mg, 0.09mmol) at rt with shaking. After shaking for 12 hours, the reaction was found complete by LCMS. The resin was drained and washed with DCM (2x10ml), DMF (3x10ml) and DCM (3x10ml) again. The product (**6**) was cleaved from

the resin through treatment with a TFA/water solution (80:20) (1.5ml) for 45 min. The resin was filtered and washed with fresh TFA/water solution (80:20) (0.5ml). The combined TFA and organic fractions were diluted with CH<sub>3</sub>CN/water (1:1) (10ml), water (2ml) and lyophilized. The crude product was purified by prep. HPLC. The crude product was dissolved in DMSO (1ml), passed through a Teflon syringe filter, and the clear filtrate was injected on a preparative HPLC. The purification used a 20x50 mm Ultro 120 C18 column running a 22 ml/min 2% gradient (AcCN/water, 0.1% TFA) for 16 min. The purified fractions were lyophilized to dryness to give 2 mg of pure product as the TFA salt (~37% yield).

**Example 29: Synthesis of 4-{4-[4-(2-Amino-4-methyl-pentanoylamino)-phenyl]-buta-1,3-diynyl}-N-(2-hydroxy-1-hydroxycarbonyl-propyl)-benzamide (7) (Continued from compound 3 of Example 27 above)**

[0311]



Reagent	MW	EQ	g/ml	mmol
Amino 1,3-diyne benzoic Thr Trt Resin (3)		1.0	125 mg	0.093
Fmoc-L-leucine	353.42	4.0	0.135 g	0.384
HATU	380	4.0	0.146 g	0.384
DIEA	129.25	8.0	133 ul	0.768
DMF			1.5 ml	

**[0312]** A solution of Fmoc-L-leucine (0.135g, 0.38mmol), HATU (0.146g, 0.38mmol) in DMF (1.5ml) was made. After 2 min. of shaking, the activated acid was added to the amino 1,3-diyne benzoic Thr Trt Resin (3) (125 mg, 0.09mmol) at rt with shaking. After shaking for 36 hours, the reaction was drained and washed with DCM (2x4ml), DMF (3x4ml) and DCM (3x4ml) again. The resin was treated with 20% piperidine in DMF (4ml) for 2 hours twice. The resin was drained and washed with DMF and DCM alternately several times. The product was cleaved from the resin through treatment with a TFA/water solution (80:20) (1.5ml) for 45 min. The resin was filtered and washed with fresh TFA/water solution (80:20) (0.5ml). The combined TFA and organic fractions were diluted with CH<sub>3</sub>CN/water (1:1) (10ml), water (2ml) and lyophilized. The crude product was purified by prep. HPLC. The crude product was dissolved in DMSO (1ml), passed through a Teflon syringe filter, and the clear filtrate was injected on a preparative HPLC. The purification used a 20x50 mm Ultro 120 C 18 column running a 22 ml/min 2% gradient (AcCN/water, 0.1% TFA) for 16 min. The purified fractions were lyophilized to dryness to give 1.7 mg of pure product (7) as the TFA salt (~30% yield).

**Examples 30-1307 of Table 1 were synthesized according to the synthetic schemes described above.**

**Biological protocols and data**

**P. aeruginosa LpxC Inhibition Assay**

**[0313]** The assay followed the general method of Hyland et al (Journal of Bacteriology 1997 179, 2029-2037: Cloning, expression and purification of UDP-3-O-acyl-GlcNAc deacetylase from *Pseudomonas aeruginosa*: a metalloamidase of the lipid A biosynthesis pathway) and the radiolabeling procedure is according to Kline *et al. supra*. Briefly, samples were incubated with 2 nM *P. aeruginosa* LpxC and 150 nM [3H-Ac]-UDP-3-O-(R-3-hydroxydecanoyl)-GlcNAc in a total volume of 50 uL for 90 min at room temperature. Reactions were carried out in 96-well polypropylene plates in 50 mM sodium phosphate buffer, pH 7.5, containing 1 mg/mL BSA. Reactions were stopped by the addition of 180 uL of a 3%

suspension of activated charcoal powder in 100 mM sodium acetate, pH 7.5. Supernatants were clarified by centrifugation. A portion of the clarified supernatant, containing the enzymatically released [3H]-acetate, was transferred to opaque white 96-well plates containing scintillation fluid. The radioactivity was measured in a Perkin-Elmer/Wallac Trilux Microbeta counter. Control reactions to which 5 mM EDTA had been added were included with each run to determine nonspecific tritium release.

## Bacterial Screens and Cultures

**[0314]** Bacterial isolates were cultivated from -70°C frozen stocks by two consecutive overnight passages at 35°C in ambient air on 5% blood agar (Remel, Lenexa, KS). Clinical isolates tested were from a collection composed of isolates collected during clinical trials and recent clinical isolates obtained from various geographically diverse hospitals in the US. Quality control and primary panel strains were from the American Type Culture Collection (ATCC; Rockville, MD), with the exception of *P. aeruginosa* PA0200, a strain with a deletion of the *mexABoprM* genes that was received from Dr. H. Schweizer. This strain does not express the principal multidrug efflux pump and is hypersusceptible to many antibacterials. Strain Z61 (ATCC 35151) is also hypersusceptible to antibacterials. It is thought that the hypersusceptibility of this strain is the result of increased permeability of its outer membrane (Angus BL et al, *Antimicrobial Agents and Chemotherapy* 1982 21, 299-309: Outer membrane permeability in *Pseudomonas aeruginosa*: Comparison of a wild-type with an antibacterial-supersusceptible mutant).

## Susceptibility Testing

**[0315]** Minimum Inhibitory Concentrations (MICs) were determined by the broth microdilution method in accordance with the National Committee for Clinical Laboratory Standards (NCCLS) guidelines. In brief, organism suspensions were adjusted to a 0.5 McFarland standard to yield a final inoculum between  $3 \times 10^5$  and  $7 \times 10^5$  colony-forming units (CFU) /mL. Drug dilutions and inocula were made in sterile, cation adjusted Mueller-Hinton Broth (Remel). An inoculum volume of 100 µL was added to wells containing 100 µL of broth with 2-fold serial dilutions of drug. All inoculated microdilution trays were incubated in ambient air at 35°C for 18-24 hours. Following incubation, the lowest concentration of the drug that prevented visible growth was recorded as the MIC. Performance of the assay was monitored by the use of laboratory quality-control strains against tobramycin, that has a defined MIC spectrum, in accordance with NCCLS guidelines.

## Efficacy in mouse model of systemic *Pseudomonas aeruginosa* infection

**[0316]** Female Balb/c mice were injected intraperitoneally with 0.5 ml of a bacterial suspension containing approximately 100 times the dose that would kill 50% of animals ( $LD_{50}$ ) of *P. aeruginosa* strain PAO1 or *E. coli* ATCC 25922. At one and five hours post infection, the test compound was injected intravenously in doses ranging from 5 mg/kg to 100 mg/kg, five mice per group. Mice were observed for 5 days, and the dose of compound resulting in survival of 50% of mice ( $ED_{50}$ ) was calculated.

## Drug Combination (Synergy) Studies

### I. Principle

**[0317]** Checkerboard experiments can be performed to assess potential interactions between primary drug of interest (#1) and other related antibacterials (#2). *P. aeruginosa* ATCC 27853, *S. aureus* ATCC 29213 and other organisms can be used as challenge strains as well as selected clinical isolates. Broth microdilution format can be used to assess the activity of drug #1 and test compound alone and in combination. Two-fold dilutions of the two compounds to be tested (each bracketing the expected MIC value) are used. The fractional inhibitory concentration (FIC) was calculated as the MIC of compound #1 in combination with a second compound, divided by the MIC of compound #1 alone. A summation FIC ( $\Sigma FIC$ ) was computed for each drug combination as the sum of the individual FICs of compound #1 and #2. Synergy was defined as an  $\Sigma FIC \leq 0.5$ , indifference as an  $\Sigma FIC$  between 0.5 and 4, and antagonism as  $\Sigma FIC > 4$ . The lowest  $\Sigma FIC$  was used for the final interpretation of drug combination studies.

Interpretation of summation ( $\Sigma FIC$ )

### **[0318]**

a) Synergism,  $x \leq 0.5$



b) Indifference,  $0.5 < x \leq 4$

c) Antagonism,  $x > 4$

[0319] Examples below marked with \* do not form part of the present invention but are included for reference purposes.

**Table 2: Demonstration of Antibacterial activity of Select Compounds from Table 1**

Enzyme inhibitory activity	
Compound Example #	IC <sub>50</sub> (nM)
12	< 100nM
572 *	< 100 nM
481 *	< 100 nM
19	< 100 nM
516 *	< 100 nM
280 *	< 100 nM
366 *	< 100 nM
777	< 100 nM
315	< 100 nM
779 *	< 100 nM
860	< 100 nM
801	< 100 nM
13 *	< 100 nM

**Table 3: Antibacterial activity vs standard panel of organisms (MIC,  $\mu$ g/ml).**

<b>MIC Key</b> MIC's of 6.25 ug/ml or less = A MIC's of greater than 6.25 ug/ml to 50 ug/ml = B MIC's of greater than 50 ug/ml = C					
Bacterial strain :	P. aeruginosa 27853	E. coli 25922	S. aureus 29213	hyper-permeable P. aerug. 35151	P. aeruginosa PAO200 mexAB
Compound Example #					
12	A	A	C	A	A
572 *	A	A	C	A	A
481 *	A	A	C	A	A
19	A	A	B	A	A
516 *	A	A	C	A	A
280 *	A	A	C	A	A
366 *	A	A	C	A	A
777	A	A	C	A	A
315	A	A	C	A	A
779 *	A	A	C	A	A

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(continued)

## MIC Key

MIC's of 6.25 ug/ml or less = A

MIC's of greater than 6.25 ug/ml to 50 ug/ml = B

MIC's of greater than 50 ug/ml = C

Bacterial strain :	<i>P. aeruginosa</i> 27853	<i>E. coli</i> 25922	<i>S. aureus</i> 29213	hyper-permeable <i>P. aerug.</i> 35151	<i>P. aeruginosa</i> PAO200 mexAB
Compound Example #					
860	A	A	C	A	A
801	A	A	C	A	A
13 *	A	A	C	AA	A

Table 4: Antibacterial activity vs cystic fibrosis isolates of *Pseudomonas aeruginosa* (MIC, µg/ml). Strains have the following phenotypes: 3198 and 3236, sensitive to most antibacterials; 2196, resistant to ciprofloxacin; 3224, resistant to ceftazidime; 3317, resistant to aztreonam; 1145 and 3206, multi-drug resistant. MIC Key

MIC's pf 6.25 ug/ml or less = A MIC's of greater than 6.25 ug/ml to 50 ug/ml = B MIC's of greater than 50 ug/ml = C								
Strain number:	3198	3236	2196	3224	3232	3317	1145	3206
Phenotype:	Sensitive	Sensitive	Cipro R	Tobra R	Ceftaz. R	Aztr. R	MDR	MDR
LpxC inhibitors								
12	A	A	B	A	A	A	A	A
481 *	A	A	A	A	A	A	A	A
19	A	A	A	A	A	A	A	A
516 *	A	A	A	A	A	A	A	A
280 *	A	A	B	A	A	A	A	A
366 *	A	A	A	A	A	A	A	A
777	A	A	A	A	A	A	A	A
315	A	A	A	A	A	A	A	A
779 *	A	A	A	A	A	A	A	A
801	A	A	A	A	A	A	A	A
13 *	A	A	A	A	A	A	A	A
Comparator antibacterials								
Tobramycin	2	0.5	2	64	1	2	8-32	64
Aztreonam	1	0.5	1	1	1	64	>128	> 128
Ceftazidime	2	0.25	2	2	64	4	>128	> 128
Cefepime	4	2	2	8	2	8	>128	32
Ciprofloxacin	1	0.06	> 8	2	2	0.5	4	>8

**Table 5: Antibacterial activity vs non-CF clinical isolates of *P. aeruginosa* and vs other gram-negative pathogens. Set 1: non-fermenting organisms. *P. aer.*, *P. aeruginosa*; *Acinet. calc.*, *Acinetobacter calcoaceticus*; *Alcal. xyl.*, *Alcaligenes xylosoxidans*; *B. cep.*, *Burkholderia cepacia*; *S. malt.*, *Stenotrophomonas maltophilia***

<b>MIC Key</b> MIC's of 6.25 ug/ml or less = A MIC's of greater than 6.25 ug/ml to 50 ug/ml = B MIC's of greater than 50 ug/ml = C								
Species:	<i>P. aer</i> 27853	<i>P. aer.</i> PAO1	<i>P. aer</i> 12307	<i>P. aer</i> psa- 6b	<i>Acinet.</i> calc.	<i>Alcal. xyl</i>	<i>B. cepacia</i>	<i>S. malt.</i>
LpxC inhibitors								
12	A	A	A	A	A	A	B	A
481 *	A	A	A	A	C	C	B	C
19	A		A	A	A		B	B
516 *	A		A	A	C	C	C	C
280 *	A	A	A	A	C	B	B	B
366 *	A	A	A	B	C	A	B	B
777	A		A	B	A	B	A	C
315	A	A	A	A	C	B	A	A
779 *	A	A		A	C	A	A	B
801	A	A		A	B	C	B	C
13 *	A	A		A	C	A	A	B
<b>Comparator antibacterials</b>								
Tobramycin			8	2	2	64	64/>128	0.5
Aztreonam			16	32	32	32	64	> 128/16
Ceftazidime			4	64	16	1	8/4	1
Cefepime			2	8	8	8	32/16	8/1
Meropenem			0.5	0.25	4	0.5	4	64
Pip/Tazo			4	>128	8	1	64	16
Ciprofloxacin					0.5	2	0.5	0.5

**Table 6: Antibacterial activity vs non-CF clinical isolates of *P. aeruginosa* and vs other gram-negative pathogens, continued. Set 2: enteric organisms. *E. aer.*, *Enterobacter aerogenes*; *E. clo.*, *Enterobacter cloacae*; *E. coli*, *Escherichia coli*; *K. pneu.*, *Klebsiella pneumoniae*; *K. oxy.*, *Klebsiella oxytoca*; *P. mir.*, *Proteus mirabilis*; *S. marc.*, *Serratia marcescens*.**

<b>MIC Key</b> MIC's of 6.25 ug/ml or less = A MIC's of greater than 6.25 ug/ml to 50 ug/ml = B MIC's of greater than 50 ug/ml = C								
Species:	<i>E. aer.</i>	<i>E. clo.</i>	<i>E. coli</i> 1619	<i>E. coli</i> 2788	<i>K. pneu.</i>	<i>K. oxy.</i>	<i>P. mir.</i>	<i>S. marc.</i>
LpxC inhibitors								
12	C	A	A	A	A	A	A	A
481 *	C	A	A	A	A	A	A	A

(continued)

<b>MIC Key</b>									
MIC's of 6.25 ug/ml or less = A									
MIC's of greater than 6.25 ug/ml to 50 ug/ml = B									
MIC's of greater than 50 ug/ml = C									
<b>Species:</b>	<b>E. aer.</b>	<b>E. clo. E.</b>	<b>coli 1619</b>	<b>E. coli 2788</b>	<b>K. pneu.</b>	<b>K. oxy.</b>	<b>P. mir.</b>	<b>S. marc.</b>	
<b>LpxC inhibitors</b>									
19	A	A	A	A	A	A	A	A	
516 *	C	B	A	B	C	C	C	A	
280 *	C	A	A	A	B	C	B	B	
366 *	C	A	A	A	B	B	A	A	
777	B	A	A	A	A	A	A	A	
315	C	A	A	A	C	C	C	B	
779 *	C	A	A	A	B	B	B	A	
801	B	A	A	A	A	A	A	A	
13 *	C	A	A	A	A	A	A	A	
<b>Comparator antibacterials</b>									
Tobramycin	64	0.06	16/64	0.06/2	64	1	2	2	
Aztreonam		<= 0.13	128/64	<= 0.13/0.25	2	0.5	<= 0.13	<= 0.13	
Ceftazidime	32	0.25	> 128	0.25/<=0.13	8	0.25	<= 0.13	0.25	
- Cefepime		<= 0.13	4/<=0.13	<= 0.13	8	<= 0.13	<= 0.13	<= 0.13	
Meropenem	2	<= 0.06	0.25/0.13	<= 0.06	0.13	<= 0.06	0.5	0.13	
Pip/Tazo		2	> 128	1	> 128	2	0.25	1	
Ciprofloxacin	> 8	0.015	2	0.03	0.06	0.03	0.03	0.25	

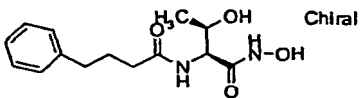
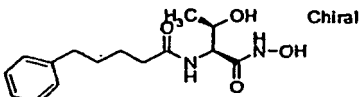
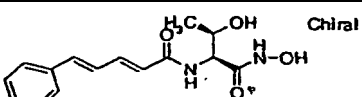
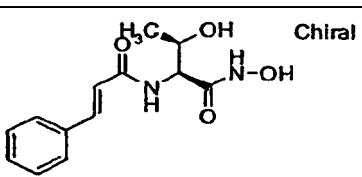
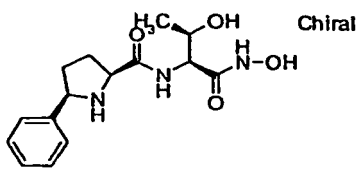
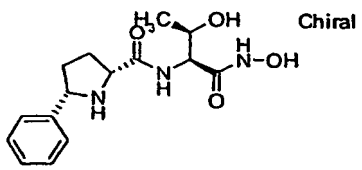
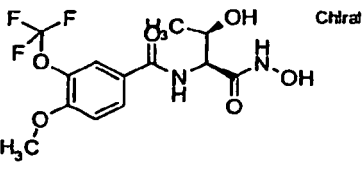
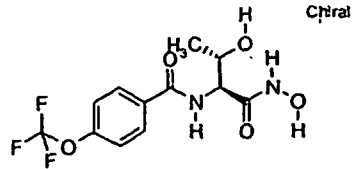
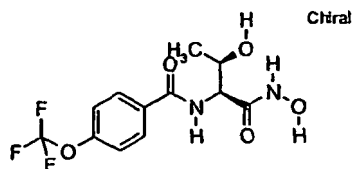
**Table 7: Drug Combination (Synergy) Studies Result**

Minimum Concentration (mg/ml) required to inhibit growth of E. coli 25922		
	Erythromycin	LpxC inhibitor 925 *
LpxC inhibitor 925 * only	-	6.25
Erythromycin only	128	-
LpxC inhibitor 925 * +erythromycin	2	0.78

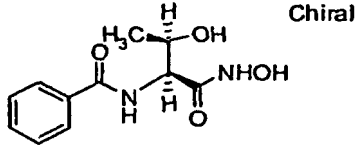
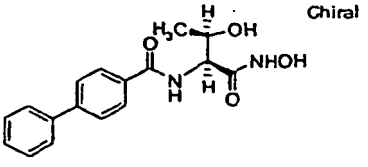
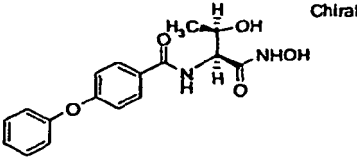
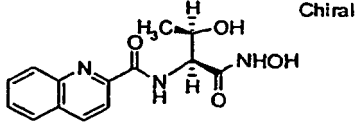
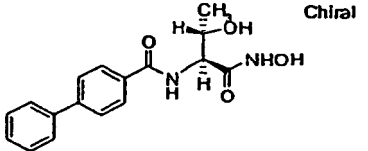
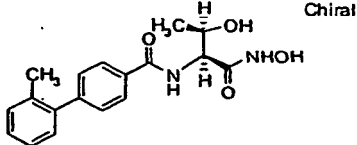
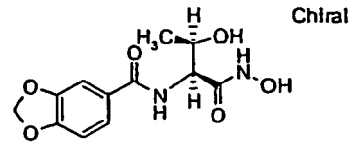
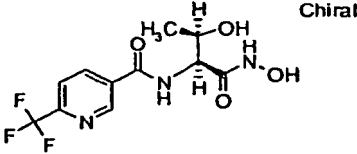
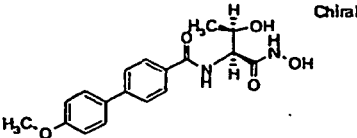
**[0320]** Each of the Example compounds of Table 1 was synthesized and assayed as described above. Many of the Example compounds 1-1307 displayed an IC<sub>50</sub> value of less than 10  $\mu$ M with respect to LpxC. Many of these compounds displayed an IC<sub>50</sub> value of less than or equal to 1  $\mu$ M or less than or equal to 0.1  $\mu$ M. Many of these compounds exhibited IC<sub>50</sub> values of less than or equal to 0.050  $\mu$ M, less than or equal to 0.030  $\mu$ M, less than or equal to 0.025  $\mu$ M, or less than or equal to 0.010  $\mu$ M.

**[0321]** It should be understood that the organic compounds according to the invention may exhibit the phenomenon of tautomerism. As the chemical structures within this specification can only represent one of the possible tautomeric forms, it should be understood that the invention encompasses any tautomeric form of the drawn structure.

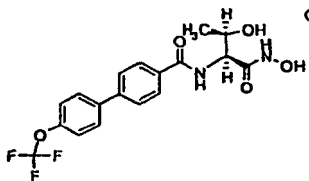
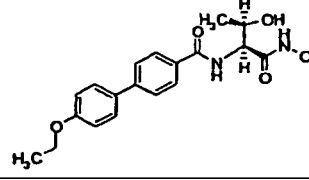
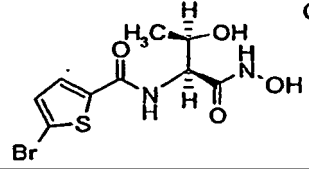
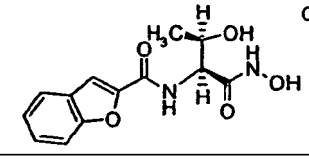
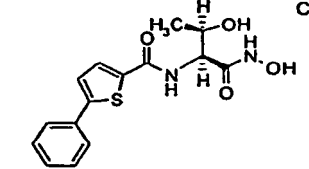
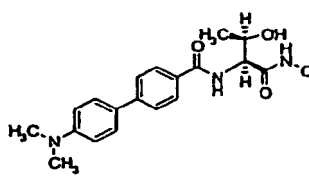
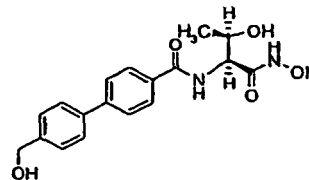
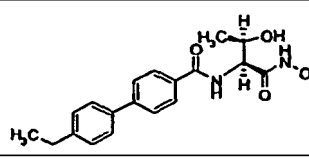
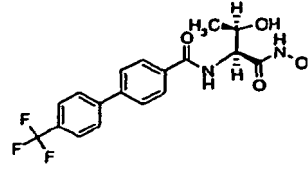
**[0322]** Examples marked with \* do not form part of the present invention and are included for reference purposes.

TABLE 1			
Example	Structure	Name	MH+
31		(2S,3R)-N,3-dihydroxy-2-[(4-phenylbutanoyl)amino]butanamide	281.3
33		N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-5-phenylpentanamide	295.3
34		(2E,4E)-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-5-phenylpenta-2,4-dienamide	291.3
35		(2E)-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-3-phenylprop-2-enamide	265.3
Example	Structure	Name	MH+
50		(2S,5R)-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-5-phenylpyrrolidine-2-carboxamide	308.3
51		(2R,5S)-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-5-phenylpyrrolidine-2-carboxamide	308.3
145		N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-4-(methoxy)-3-[(trifluoromethyl)oxy]benzamide	353.3
146		N-[(1S,2S)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-4-[(trifluoromethyl)oxy]benzamide	323.2
147		N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-4-[(trifluoromethyl)oxy]benzamide	323.2

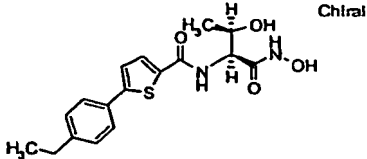
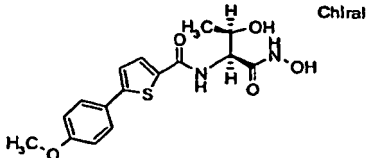
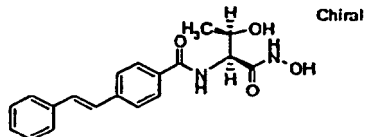
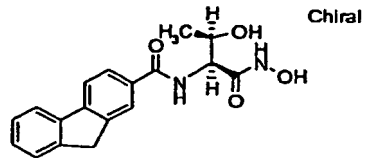
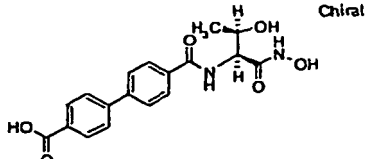
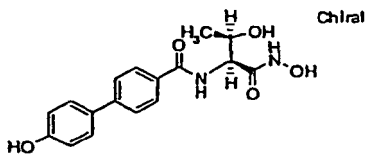
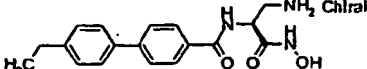
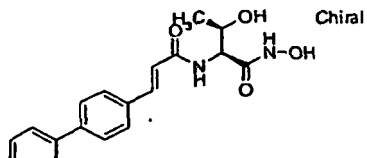
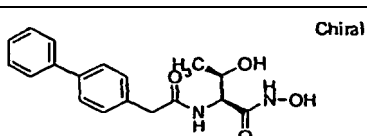
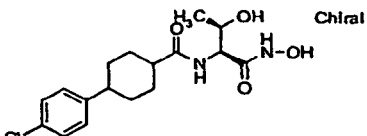
(continued)

Example	Structure	Name	MH+
154		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	239.2
155		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-1,1'-biphenyl-4-carboxamide	315.3
161		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-(phenyloxy)benzamide	331.3
166		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)quinoline-2-carboxamide	290.3
168		N-((1S,2S)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-1,1'-biphenyl-4-carboxamide	315.3
169		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-2'-methyl-1,1'-biphenyl-4-carboxamide	329.4
174		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-1,3-benzodioxole-5-carboxamide	283.3
175		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-6-(bifluoromethyl)pyridine-3-carboxamide	308.2
183		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4'-(methoxy)-1,1'-biphenyl-4-carboxamide	345.4

(continued)

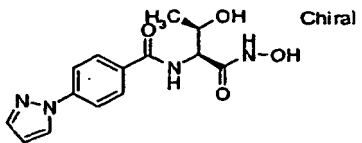
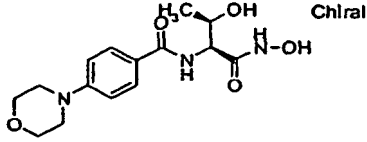
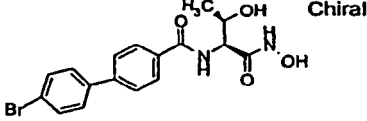
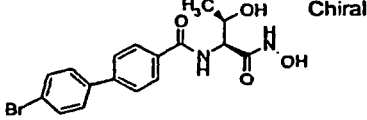
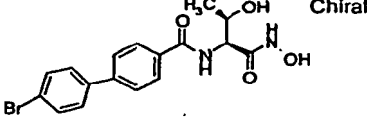
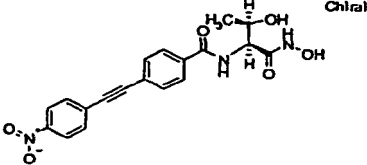
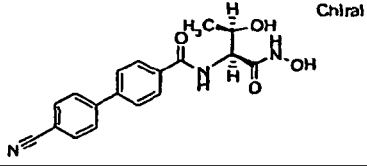
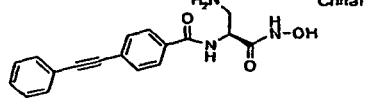
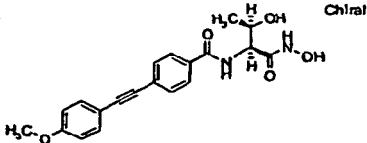
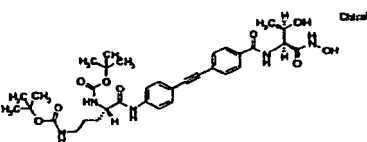
Example	Structure	Name	MH+
184		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4'-[(trifluoromethyl)oxy]-1,1'-biphenyl-4-carboxamide	399.3
185		4'-(ethoxy)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-1,1'-biphenyl-4-carboxamide	359.4
193		5-bromo-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)thiophene-2-carboxamide	324.2
195		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-1-benzofuran-2-carboxamide	279.3
196		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-5-phenylthiophene-2-carboxamide	321.4
197		4'-(dimethylamino)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-1,1'-biphenyl-4-carboxamide	358.4
202		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4'-(hydroxymethyl)-1,1'-biphenyl-4-carboxamide	345.4
207		4'-ethyl-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-1,1'-biphenyl-4-carboxamide	343.4
208		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4'-(trifluoromethyl)-1,1'-biphenyl-4-carboxamide	383.3

(continued)

Example	Structure	Name	MH+
209		5-(4-ethylphenyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)thiophene-2-carboxamide	349.4
210		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-5-[4-(methoxy)phenyl]thiophene-2-carboxamide	351.4
216		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[(E)-2-phenylethenyl]benzamide	341.4
217		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-9H-fluorene-2-carboxamide	327.4
218		4'-[(((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)amino)carbonyl]-1,1'-biphenyl-4-carboxylic acid	359.3
221		4'-hydroxy-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-1,1'-biphenyl-4-carboxamide	331.3
280 *		N-[(1S)-1-(aminomethyl)-2-(hydroxyamino)-2-oxoethyl]-4'-ethyl-1,1'-biphenyl-4-carboxamide	328.4
299		(2E)-3-(1,1'-biphenyl-4-yl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)prop-2-enamide	341.4
300		(2S,3R)-2-[(1,1'-biphenyl-4-ylacetyl)amino]-N,3-dihydroxybutanamide	329.4
308		4-(4-chlorophenyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)cyclohexanecarboxamide	355.8



(continued)

Example	Structure	Name	MH+
309		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-(1H-pyrazol-1-yl)benzamide	305.3
310		N-(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-morpholin-4-ylbenzamide	324.3
315		4'-bromo-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-1,1'-biphenyl-4-carboxamide	394.2
316		4'-bromo-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-1,1'-biphenyl-4-carboxamide	394.2
317		4'-bromo-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-1,1'-biphenyl-4-carboxamide	394.2
322		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[(4-nitrophenyl)ethynyl]benzamide	384.4
326		4'-cyano-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-1,1'-biphenyl-4-carboxamide	340.3
366		N-[(1S)-1-(aminomethyl)-2-(hydroxyamino)-2-oxoethyl]-4-(phenylethynyl)benzamide	324.4
370		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[(4-(methoxy)phenyl)ethynyl]benzamide	369.4
374		1,1-dimethylethyl (1S)-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-1-({[4-({4-({[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl}amino)carbonyl]phenyl}ethynyl]phenyl}amino)carbonyl)butylcarbamate	668.8

(continued)

Example	Structure	Name	MH+
407		N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)-4-((4-(trifluoromethyl)phenyl)ethynyl)benzamide	407.4
419		4-((4-(((2S)-2,5-diaminopentanoyl)amino)phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)benzamide	468.5
439		4-((3-aminophenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)benzamide	354.4
442		4-((4-((aminoacetyl)amino)phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)benzamide	411.4
447		4-((4-aminophenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)benzamide	354.4
469		N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)-4-((4-((morpholin-4-yl)acetyl)amino)phenyl)ethynyl)benzamide	481.5
471		N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)-4-((4-((trifluoromethoxy)phenyl)ethynyl)benzamide	423.4
481*		N-[(1S)-1-(aminomethyl)-2-(hydroxyamino)-2-oxoethyl]-4-(4-phenylbuta-1,3-diynyl)benzamide	348.4
489		N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)-4-((3-hydroxyphenyl)ethynyl)benzamide	355.4

(continued)

Example	Structure	Name	MH+
491		4-[[4-(([(cyanomethyl)amino]acetyl)amino)phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	450.5
494		4-[(4-chlorophenyl)ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	373.8
495		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[(4-methylphenyl)ethynyl]benzamide	353.4
497		4-[(3-fluorophenyl)ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	357.4
498		4-[(4-fluorophenyl)ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	357.4
499		4-[(4-(([(cyclopropylamino)acetyl]amino)phenyl)ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	451.5
500		4-({4-[(2-(dimethylamino)ethyl)amino]acetyl}amino)phenyl]ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	482.6
501		4-({4-[(2-(acetylamino)ethyl)amino]acetyl}amino)phenyl]ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	496.5
502		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-({4-[(3-(2-oxopyrrolidin-1-yl)propyl)amino]acetyl}amino)phenyl]ethynyl)benzamide	536.6
503		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-({4-[(pyridin-3-ylmethyl)amino]acetyl}amino)phenyl]ethynyl)benzamide	502.5
504		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-({4-[(2-pyridin-2-ylethyl)amino]acetyl}amino)phenyl]ethynyl)benzamide	516.6
505		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-({4-[(4-methylpiperazin-1-yl)acetyl]amino}phenyl]ethynyl)benzamide	494.6
506		4-({4-[(1,4'-bipiperidin-1'-yl)acetyl]amino}phenyl]ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	562.7

(continued)

Example	Structure	Name	MH+
507		1-(2-[[4-({4-[[{(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl} amino)carbonyl]phenyl} ethynyl)phenyl]amino}-2-oxoethyl)piperidine-4-carboxamide	522.6
508		N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-4-[[4-[(piperidin-3-ylamino)acetyl]amino]phenyl]ethynyl]benzamide	494.6
509		N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-4-[[4-[(piperidin-4-ylamino)acetyl]amino]phenyl]ethynyl]benzamide	494.6
510		-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-4-[[4-[(piperidin-2-ylmethyl)amino]acetyl]amino]phenyl]ethynyl] benzamide	508.6
511		N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-4-[[4-[(piperidin-3-ylmethyl)amino]acetyl]amino]phenyl]ethynyl] benzamide	508.6
512		4-[[4-[(3-aminopyrrolidin-1-yl)acetyl]amino]phenyl]ethynyl]-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	480.5
513		4-[(4-[(azepan-1-ylacetyl)amino]phenyl]ethynyl)-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]beazamide	493.6
514		N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-4-[[4-[(4-morpholin-4-ylphenyl)amino]acetyl]amino]phenyl]ethynyl] benzamide	572.6
516 *		N-[(1S)-1-(aminomethyl)-2-(hydroxyamino)-2-oxoethyl]-4-[[4-[(cyclopropylamino)acetyl]amino]phenyl]eth ynyl]benzamide	436.5
521		4-[[4-[(2-hydroxyethyl)amino]acetyl]amino]phenyl]eth ynyl]-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	455.5
522		N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-4-[(4-[(2-(methyloxy)ethyl)amino]acetyl]amino]phenyl] ethynyl]benzamide	469.5
523		N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-4-[(4-[(methyl[2-(methyloxy)ethyl]amino]acetyl]amino]phenyl] ethynyl] benzamide	483.5
524		4-[[4-[(2-(dimethylamino)ethyl)(methyl)amino]acetyl] a mino]phenyl]ethynyl]-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl] benzamide	496.6

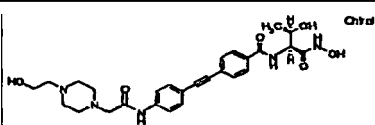
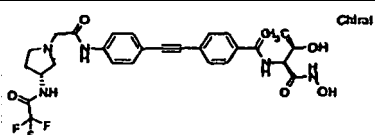
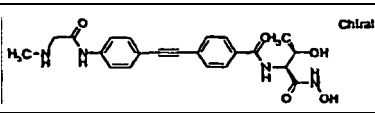
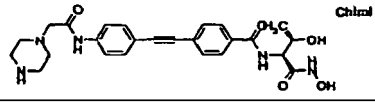
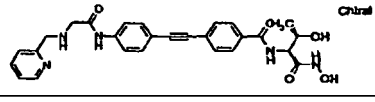
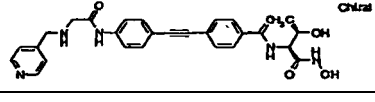
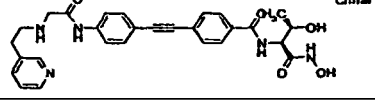
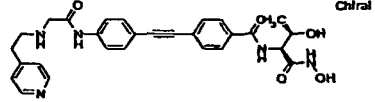
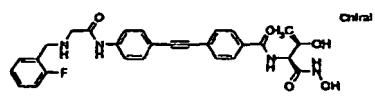
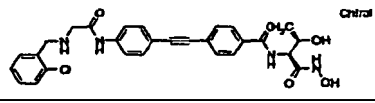
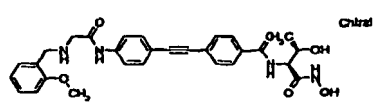
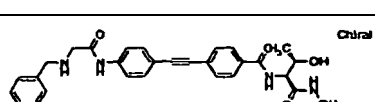
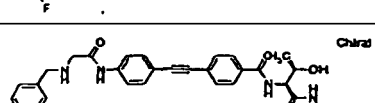
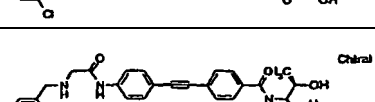
(continued)

Example	Structure	Name	MH+
525		4-([4-([(3R)-3-(dimethylamino)pyrrolidin-1-yl]acetyl)amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	508.6
526		4-([4-([(3S)-3-(dimethylamino)pyrrolidin-1-yl]acetyl)amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	508.6
527		4-([4-([(3R)-3-(acetylamino)pyrrolidin-1-yl]acetyl)amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	522.6
528		4-([4-([(3S)-3-(acetylamino)pyrrolidin-1-yl]acetyl)amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	522.6
529		4-([4-([(3R)-1-azabicyclo[2.2.2]oct-3-ylamino]acetyl)amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	520.6
530		4-([4-([(3S)-1-azabicyclo[2.2.2]oct-3-ylamino]acetyl)amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	520.6
531		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-([(2R)-pyrrolidin-2-ylmethyl]amino)acetyl)amino]phenyl)ethynyl)benzamide	494.6
532		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-([(2S)-pyrrolidin-2-ylmethyl]amino)acetyl)amino]phenyl)ethynyl)benzamide	494.6
533		4-([4-([(3-aminocyclohexyl)amino]acetyl)amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	508.6
534		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-([(3-hydroxypiperidin-1-yl)acetyl]amino]phenyl)ethynyl)benzamide	495.5
535		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-([(3-morpholine-4-ylpropyl)amino]acetyl)amino]phenyl)ethynyl)benzamide	538.6
536		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-([(2-methylpropyl)amino]acetyl)amino]phenyl)ethynyl)benzamide	467.5
537		4-([4-([(ethylamino)acetyl]amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	439.5

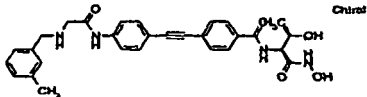
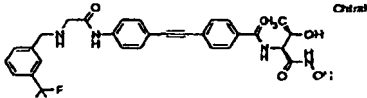
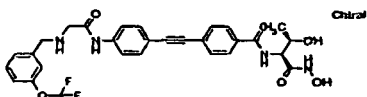
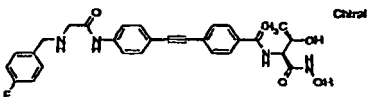
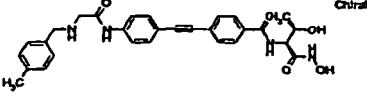
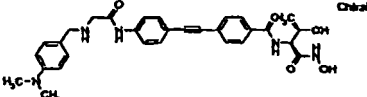
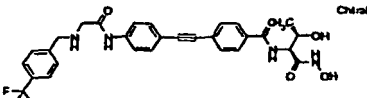
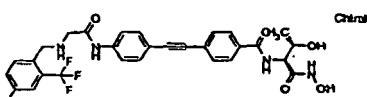
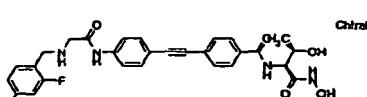
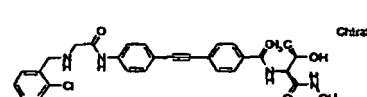
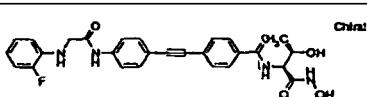
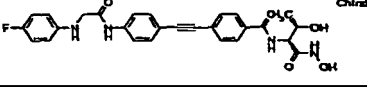
(continued)

Example	Structure	Name	MH+
538		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-({4-[(piperidin-1-ylacetyl)amino]phenyl} ethynyl)benzamide	479.5
539		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-1-({4-[(3-hydroxypropyl)amino]acetyl}amino)phenyl} ethynyl)benzamide	469.5
540		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-({4-[(3-methoxypropyl)amino]acetyl}amino)phenyl} ethynyl)benzamide	483.5
541		4-([4-[(2-cyanoethyl)amino]acetyl}amino)phenyl} ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	464.5
542		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-[(2-pyrrolidin-1-ylethyl)amino]acetyl}amino)phenyl} ethynyl)benzamide	508.6
543		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-[(2-methyl-1H-imidazol-1-yl)acetyl]amino]phenyl} ethynyl)benzamide	476.5
572 *		N-[(1S)-1-(aminomethyl)-2-(hydroxyamino)-2-oxoethyl]-4-([4-[(phenylamino)acetyl]amino]phenyl} ethynyl)benzamide	472.5
576		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-({4-[(1H-imidazol-1-ylacetyl)amino]phenyl} ethynyl)benzamide	462.5
577		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-[(phenylamino)acetyl]amino]phenyl} ethynyl)benzamide	487.5
578		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-({4-[(2-phenylethyl)aminolacetyl]amino}phenyl} ethynyl)benzamide	515.6
579		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-[(3-phenylpropyl)amino]acetyl]amino)phenyl} ethynyl)benzamide	529.6
583		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-[(2-[4-(phenylmethyl)piperazin-1-yl]ethyl)amino]acetyl]amino]phenyl} ethynyl)benzamide	613.7
584		4-([4-[(aminoacetyl)amino]acetyl]amino)phenyl} ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	468.5

(continued)

Example	Structure	Name	MH+
585		4-([4-([4-(2-hydroxyethyl)piperazin-1-yl]acetyl)amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	524.6
586		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-([3-(trifluoroacetyl)amino]pyrrolidin-1-yl)acetyl]amino)phenyl)ethynyl)benzamide	576.5
587		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-([4-[(methylamino)acetyl]amino]phenyl)ethynyl]benzamide	425.5
588		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-([4-(piperazin-1-ylacetyl)amino]phenyl)ethynyl]benzamide	480.5
589		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-([4-([pyridin-2-ylmethyl]amino)acetyl]amino)phenyl)ethynyl)benzamide	502.5
590		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-([4-([pyridin-4-ylmethyl]amino)acetyl]amino)phenyl)ethynyl)benzamide	502.5
591		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-([4-([2-pyridin-3-ylethyl]amino)acetyl]amino)phenyl)ethynyl)benzamide	516.6
592		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-([4-([2-pyridin-4-ylethyl]amino)acetyl]amino)phenyl)ethynyl)benzamide	516.6
593		4-([4-([4-([2-fluorophenyl]methyl)amino]acetyl)amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	519.5
594		4-([4-([4-([2-chlorophenyl]methyl)amino]acetyl)amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	536.0
595		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-([4-([2-methoxyphenyl]methyl)amino]acetyl]amino)phenyl)ethynyl)benzamide	531.6
596		4-([4-([4-([3-fluorophenyl]methyl)amino]acetyl)amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	519.5
597		4-([4-([4-([3-chlorophenyl]methyl)amino]acetyl)amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	536.0
598		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-([4-([3-methoxyphenyl]methyl)amino]acetyl]amino)phenyl)ethynyl)benzamide	531.6

(continued)

Example	Structure	Name	MH+
599		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-({4-[[[(3-methylphenyl)methyl]amino]acetyl}amino]phenyl)ethynyl)benzamide	515.6
600		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-({4-[[[(3-(trifluoromethyl)phenyl)methyl]amino]acetyl}amino]phenyl)ethynyl)benzamide	569.5
601		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-({4-[[[(3-[(trifluoromethoxy)methyl]phenyl)methyl]amino]acetyl}amino]phenyl)ethynyl)benzamide	585.5
602		4-({4-[[[(4-fluorophenyl)methyl]amino]acetyl}amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	519.5
603		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-({4-[[[(4-methylphenyl)methyl]amino]acetyl}amino]phenyl)ethynyl)benzamide	515.6
604		4-({4-[[[(4-(dimethylamino)phenyl)methyl]amino]acetyl}amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	544.6
605		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-({4-[[[(4-(trifluoromethyl)phenyl)methyl]amino]acetyl}amino]phenyl)ethynyl)benzamide	569.5
606		4-({4-[[[(4-fluoro-2-(trifluoromethyl)phenyl)methyl]amino]acetyl}amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	587.5
607		4-({4-[[[(2,4-difluorophenyl)methyl]amino]acetyl}amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	537.5
608		4-({4-[[[(2,4-dichlorophenyl)methyl]amino]acetyl}amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	570.4
609		4-({4-[[[(2-fluorophenyl)methyl]amino]acetyl}amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	505.5
610		4-({4-[[[(4-fluorophenyl)methyl]amino]acetyl}amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	505.5



(continued)

Example	Structure	Name	MH+
611		4-({4-([[(3,5-difluorophenyl)methyl]amino)acetyl]amino}phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	537.5
612		4-([4-({[(4-bromophenyl)amino]acetyl}amino)phenyl]ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	566.4
613		4-({4-([[(4-(dimethylamino)phenyl)amino]acetyl]amino}phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	530.6
629		4-([4-([[(2S)-2-amino-4-methylpentanoyl]amino]phenyl)ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	467.5
630		4-([4-([[(2S)-2-amino-4-cyanobutanoyl]amino]phenyl)ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	464.5
631		4-([4-([[(2S)-2,3-diaminopropanoyl]amino]phenyl)ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	440.5
634		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-(pyrazin-2-ylethynyl)benzamide	341.3
635		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-({4-([[(3-(1H-imidazol-1-yl)propyl]amino)acetyl]amino}phenyl)ethynyl)benzamide	519.6
637		4-({4-([[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]amino)carbo nyl]phenyl)ethynyl)benzoic acid	383.4
638		N-(2-([4-({4-([[(1S,2R)-2-hydroxy-1-[(hydroxyaminocarbonyl]propyl]amino)carbo nyl]phenyl)ethynyl)phenyl]amino)-2-oxoethyl)-1,3-benzodioxole-4-carboxamide	559.5
639		4-({4-([[(2R)-2-([[(2R)-2,5-diaminopentanoyl]amino)-4-phenylbutanoyl]amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	629.7

(continued)

Example	Structure	Name	MH+
640		4-[(4-[[[(2R)-2-amino-4-phenylbutanoyl]amino]phenyl]ethynyl]-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	515.6
641		4-[(4-[[[(2S)-2-amino-3-phenylpropanoyl]amino]phenyl]ethynyl]-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	501.6
642		4-[(4-[[[(2-aminoethyl)amino]acetyl]amino]phenyl]ethynyl]-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	454.5
644		4-[(4-[[[(cyclobutylamino)acetyl]amino]phenyl]ethynyl]-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	465.5
645		4-[(4-[[[(cyclopentylamino)acetyl]amino]phenyl]ethynyl]-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	479.5
646		4-[(4-[[[(cyclohexylamino)acetyl]amino]phenyl]ethynyl]-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	493.6
647		4-[(4-[[[(cycloheptylamino)acetyl]amino]phenyl]ethynyl]-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	493.6
648		4-[(4-[[[(cyclooctylamino)acetyl]amino]phenyl]ethynyl]-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	521.6
649		N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-4-[(4-[[[(propylamino)acetyl]amino]phenyl]ethynyl]benzamide	453.5
650		4-[(4-[[[(hexylamino)acetyl]amino]phenyl]ethynyl]-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	495.6
651		N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-4-[(4-[[[(1-methylethyl)amino]acetyl]amino]phenyl]ethynyl]benzamide	453.5
652		4-[(4-[[[(1,1-dimethylethyl)amino]acetyl]amino]phenyl]ethynyl]-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	467.5

(continued)

Example	Structure	Name	MH+
653		4-[[4-({[ethyl(methyl)amino]acetyl}amino)phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	453.5
654		4-[[4-({[diethylamino]acetyl}amino)phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	467.5
655		4-[[4-({[1,1-dimethylethyl(methyl)amino]acetyl}amino)phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	481.6
656		4-[[4-({[cyclohexyl(methyl)amino]acetyl}amino)phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	507.6
657		4-[[4-({[bis(1-methylethyl)amino]acetyl}amino)phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	495.6
658		4-[[4-({[(cyclohexylmethyl)amino]acetyl}amino)phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	507.6
659		4-[[4-({[(2,3-dimethylcyclohexyl)amino]acetyl}amino)phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	521.6
660		4-[[4-({[(1R,2R,4S)-bicyclo[2.2.1]hept-2-ylamino]acetyl}amino)phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	505.6
661		4-[[4-({[(1S,2R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]methylamino)acetyl}amino)phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	547.7
662		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[[4-({[4-(trifluoromethyl)piperidin-1-yl]acetyl}amino)phenyl]ethynyl]benzamide	547.5
721		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[[4-({[pyridin-2-ylamino]acetyl}amino)phenyl]ethynyl]benzamide	488.5
722		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[[4-({[pyridin-3-ylamino]acetyl}amino)phenyl]ethynyl]benzamide	488.5
723		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[[4-({[pyridin-4-ylamino]acetyl}amino)phenyl]ethynyl]benzamide	488.5

(continued)

Example	Structure	Name	MH+
724		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[(4-[(4-phenylpiperazin-1-yl)acetyl]amino)phenyl]ethynyl]benzamide	556.6
725		4-[[4-[(4-(4-fluorophenyl)piperazin-1-yl)acetyl]amino]phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	574.6
726		4-[[4-[(1-acetyl-piperidin-4-yl)(cyclopropyl)amino]acetyl]amino]phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	576.7
727		4-[(4-[(butylamino)acetyl]amino)phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	467.5
728		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[(4-[(1R)-1-phenylethyl]amino)acetyl]amino]phenyl]ethynyl]benzamide	515.6
729		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[(4-[(1S)-1-phenylethyl]amino)acetyl]amino]phenyl]ethynyl]benzamide	515.6
730		4-[[4-[(cyclopropyl(methyl)amino)acetyl]amino]phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	465.5
731		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[[4-[(methyl(phenylmethyl)amino)acetyl]amino]phenyl]ethynyl]benzamide	515.6
733		4-[(4-[(2S)-2-aminopropanoyl]amino)phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	425.5
734		4-[(4-[(2R)-2-aminopropanoyl]amino)phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	425.5
735		4-[(4-[(2S)-2-amino-3-methylbutanoyl]amino]phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	453.5
736		4-[(4-[(2S,3R)-2-amino-3-hydroxybutanoyl]amino]phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	455.5
737		(2S)-N-[4-[(4-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]amino)carbonyl]phenyl]ethynyl]phenyl]pyrrolidine-2-carboxamide	451.5
738		4-[(4-[(2S)-2-amino-3-(1H-imidazol-4-yl)propanoyl]amino]phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	491.5

(continued)

Example	Structure	Name	MH+
743		4-({4-(((2S)-2-(((2S)-2,5-diaminopentanoyl)amino)-3-phenylpropanoyl)amino)phenyl}ethynyl)-N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)benzamide	615.7
751		3,4-dihydroxy-N-(2-({4-({4-(((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)amino)carbonyl)phenyl}ethynyl)phenyl}amino)-2-oxoethyl)benzamide	547.5
752		4-({4-(((2S)-2,5-diaminopentanoyl)amino)acetyl}amino)phenyl}ethynyl)-N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)benzamide	525.6
755		3-({4-(((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)amino)carbonyl)phenyl}ethynyl)benzoic acid	383.4
756		4-({4-(((3-aminopropyl)amino)acetyl}amino)phenyl}ethynyl)-N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)benzamide	468.5
775		4-[4-(4-(((cyclopropylamino)acetyl}amino)phenyl)buta-1,3-diynyl]-N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)benzamide	475.5
776		N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)-4-(4-(4-(((piperidin-1-ylacetyl}amino)phenyl)buta-1,3-diynyl)benzamide	503.6
777		N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)-4-[4-(4-(((phenylamino)acetyl}amino)phenyl)buta-1,3-diynyl]benzamide	511.5
778		N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)-4-[4-(4-(((phenylmethyl)amino)acetyl}amino)phenyl)buta-1,3-diynyl]benzamide	525.6
779 *		N-((1S,2R)-2-amino-1-((hydroxyamino)carbonyl)propyl)-4'-ethyl-1,1' biphenyl-4-carboxamide	342.4
780		4-({4-(((dimethylamino)acetyl}amino)phenyl}ethynyl)-N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)benzamide	439.5
781		N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)-4-({4-(((pyrrolidin-1-ylacetyl}amino)phenyl}ethynyl)benzamide	465.5
782		N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)-4-({4-(((pentylamino)acetyl}amino)phenyl}ethynyl)benzamide	481.6

(continued)

Example	Structure	Name	MH+
783		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[[4-([[(thien-2-ylmethyl)amino]acetyl]amino)phenyl]ethynyl] benzamide	507.6
784		4-[[4-([[(1H-benzimidazol-2-ylmethyl)amino]acetyl]amino)phenyl]ethynyl] N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl) benzamide	541.6
785		4-[[4-([[(1-benzothien-3-ylmethyl)amino]acetyl]amino)phenyl]ethynyl] N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	557.6
786		4-(4-[4-([[(2-fluorophenyl)methyl]amino]acetyl]amino]phenyl)buta-1,3-diynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl) benzamide	543.6
787		4-(4-[4-([[(3-fluorophenyl)methyl]amino]acetyl]amino]phenyl)buta-1,3-diynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl) benzamide	543.6
788		4-(4-[4-([[(4-fluorophenyl)methyl]amino]acetyl]amino]phenyl)buta-1,3-diynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl) benzamide	543.6
789		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-(4-[4-([[(2-methylphenyl)methyl]amino]acetyl]amino]phenyl)buta-1,3-diynyl)benzamide	539.6
790		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-(4-[4-([[(3-methylphenyl)methyl]amino]acetyl]amino]phenyl)buta-1,3-diynyl)benzamide	539.6
791		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-(4-[4-([[(4-methylphenyl)methyl]amino]acetyl]amino]phenyl)buta-1,3-diynyl)benzamide	539.6
792		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[4-([[(pyridin-2-ylmethyl)amino]acetyl]amino)phenyl]buta-1,3-diynyl benzamide	526.6
793		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[4-([[(pyridin-3-ylmethyl)amino]acetyl]amino)phenyl]buta-1,3-diynyl benzamide	526.6
794		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[4-([[(pyridin-4-ylmethyl)amino]acetyl]amino)phenyl]buta-1,3-diynyl benzamide	526.6

(continued)

Example	Structure	Name	MH+
795		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[4-(4-[[[2-(methoxy)phenyl]methyl]amino)acetyl]amin o)phenyl]buta-1,3-diynyl]benzamide	555.6
796		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[4-(4-[[[3-(methoxy)phenyl]methyl]amino)acetyl]amin o)phenyl]buta-1,3-diynyl]benzamide	555.6
797		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[4-(4-[[[4-(methoxy)phenyl]methyl]amino)acetyl]amin o)phenyl]buta-1,3-diynyl]benzamide	555.6
798		4-[4-[4-[[[2-fluorophenyl]amino]acetyl]amino]phenyl]buta-1,3-diynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	529.5
799		4-[4-[4-[[[3-fluorophenyl]amino]acetyl]amino]phenyl]buta-1,3-diynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	529.5
800		4-[4-[4-[[[4-fluorophenyl]amino]acetyl]amino]phenyl]buta-1,3-diynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	529.5
801		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[4-(4-[[[pyridin-2-ylamino]acetyl]amino]phenyl]buta-1,3-diynyl]benzamide	512.5
802		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[4-(4-[[[pyridin-3-ylamino]acetyl]amino]phenyl]buta-1,3-diynyl]benzamide	512.5
803		N-((1S,2R)-2-hydroxy-1-[(hydroxyaminocarbonyl]propyl)-4-[4-(4-[[[pyridin-4-ylamino]acetyl]amino]phenyl]buta-1,3-diynyl]benzamide	512.5
804		4-[4-(4-[[[cyclobutylamino]acetyl]amino]phenyl]buta-1,3-diynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	489.5
805		4-[4-(4-[[[cyclopentylamino]acetyl]amino]phenyl]buta-1,3-diynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	503.6
806		4-[4-(4-[[[cyclohexylamino]acetyl]amino]phenyl]buta-1,3-diynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	517.6
807		4-[4-(4-[[[cycloheptylamino]acetyl]amino]phenyl]buta-1,3-diynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	531.6

(continued)

Example	Structure	Name	MH+
808		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[4-(4-[(methylamino)acetyl]amino)phenyl]buta-1,3-diynyl]benzamide	449.5
809		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[4-(4-[(propylamino)acetyl]amino)phenyl]buta-1,3-diynyl]benzamide	477.5
810		4-[4-(4-[(butylamino)acetyl]amino)phenyl]buta-1,3-diynyl-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	491.6
811		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[4-(4-[(pentylamino)acetyl]amino)phenyl]buta-1,3-diynyl]benzamide	505.6
812		4-[4-(4-[(hexylamino)acetyl]amino)phenyl]buta-1,3-diynyl-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	519.6
813		4-[4-(4-[(ethyl(methyl)amino)acetyl]amino)phenyl]buta-1,3-diynyl-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	477.5
814		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[4-(4-[(1-methylethyl)amino]acetyl]amino)phenyl]buta-1,3-diynyl]benzamide	477.5
815		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[4-(4-[(2-methylpropyl)amino]acetyl]amino)phenyl]buta-1,3-diynyl]benzamide	491.6
816		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[4-(4-[(2,2,2-trifluoroethyl)amino]acetyl]amino)phenyl]buta-1,3-diynyl]benzamide	517.5
817		4-[4-(4-[(2-hydroxyethyl)amino]acetyl]amino)phenyl]buta-1,3-diynyl-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	479.5
818		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[4-(4-[(2-methoxyethyl)amino]acetyl]amino)phenyl]buta-1,3-diynyl]benzamide	493.5
819		4-[4-(4-[(2-(dimethylamino)ethyl)amino]acetyl]amino)phenyl]buta-1,3-diynyl-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	506.6
820		4-[4-(4-[(2-cyanoethyl)amino]acetyl]amino)phenyl]buta-1,3-diynyl-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	488.5
821		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[4-(4-[(pyrrolidin-1-yl)acetyl]amino)phenyl]buta-1,3-diynyl]benzamide	489.5



(continued)

Example	Structure	Name	MH+
822		4-(4-{4-[(azepan-1-ylacetyl)amino]phenyl}buta-1,3-dienyl)-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	517.6
823		N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-4-[4-(4-{[(4-methylpiperazin-1-yl)acetyl]amino}phenyl)buta-1,3-dienyl]benzamide	518.6
824		N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-4-(4-{4-[(morpholin-4-ylacetyl)amino]phenyl}buta-1,3-dienyl)benzamide	505.5
825		4-[4-[4-[(cyclohexyl(methyl)amino)acetyl]amino]phenyl]buta-1,3-dienyl)-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	531.6
826		N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-4-(4-{4-[(1R)-1-phenylethyl]amino}acetyl)amino]phenyl]buta-1,3-dienyl)benzamide	539.6
827		N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-4-(4-{4-[(1S)-1-phenylethyl]amino}acetyl)amino]phenyl]buta-1,3-dienyl)benzamide	539.6
828		N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-4-[4-[4-[(2-phenylethyl)amino]acetyl]amino]phenyl]buta-1,3-dienyl)benzamide	539.6
829		N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-4-(4-{4-[(1H-imidazol-1-ylacetyl)amino]phenyl}buta-1,3-dienyl)benzamide	486.5
830		4-[4-[4-[(1R,2R,4S)-bicyclo[2.2.1]hept-2-ylamino]acetyl]amino]phenyl]buta-1,3-dienyl)-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	529.6
831		4-[4-[4-[(cyclohexylmethyl)amino]acetyl]amino]phenyl]buta-1,3-dienyl)-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	531.6
836		4-[(4-ethylphenyl)ethynyl]-N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	367.4
837		N-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-4-[(4-hydroxyphenyl)ethynyl]benzamide	355.4

(continued)

Example	Structure	Name	MH+
860		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[(4-[(pyrazin-2-ylamino)acetyl]amino)phenyl]ethynyl]benzamide	489.5
861		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[(4-[(4-phenylpiperidin-1-yl)acetyl]amino)phenyl]ethynyl]benzamide	555.6
862		4-[(4-[(4-(2-fluorophenyl)piperazin-1-yl)acetyl]amino)phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	574.6
863		4-[(4-[(1S,4R)-bicyclo[2.2.1]hept-2-ylamino]acetyl]amino)phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	505.6
864		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[(4-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]amino)acetyl]amino)phenyl]ethynyl]benzamide	547.7
865		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[(4-[(tricyclo[3.3.1.1~3,7~]dec-1-ylmethyl)amino]acetyl]amino)phenyl]ethynyl]benzamide	559.7
866		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[(4-[(4-methylcyclohexyl)amino]acetyl]amino)phenyl]ethynyl]benzamide	507.6
867		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[(4-[(2,2,2-trifluoroethyl)amino]acetyl]amino)phenyl]ethynyl]benzamide	493.5
868		4-[(4-[(2-(2-fluorophenyl)ethyl)amino]acetyl]amino)phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	533.6
869		4-[(4-[(2-(3-fluorophenyl)ethyl)amino]acetyl]amino)phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	533.6
870		4-[(4-[(2-(4-fluorophenyl)ethyl)amino]acetyl]amino)phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	533.6
871		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[(4-[(1S,2R)-2-phenylcyclopropyl]aminolacetyl]amino)phenyl]ethynyl]benzamide	527.6
872		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[(4-[(2-methylphenyl)methyl]amino)acetyl]amino)phenyl]ethynyl]benzamide	515.6

(continued)

Example	Structure	Name	MH+
873		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[[4-[[[2-(trifluoromethyl)phenyl]methyl]amino]acetyl]amino}phenyl]ethynyl]benzamide	569.5
874		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[[4-[[[2-(trifluoromethoxy)phenyl]methyl]amino]acetyl]amino}phenyl]ethynyl]benzamide	585.5
875		4-((4-[[[4-(4-chlorophenyl)methyl]amino]acetyl]amino}phenyl]ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	536.0
876		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[[4-[[[4-(4-methoxyphenyl)methyl]amino]acetyl]amino}phenyl]ethynyl]benzamide	531.6
877		4-[[4-[[[4-(1,1-dimethylethyl)phenyl]methyl]amino]acetyl]amino}phenyl]ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	557.7
878		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[[4-[[[4-(4-nitrophenyl)methyl]amino]acetyl]amino}phenyl]ethynyl]benzamide	546.5
879		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[[4-[[[4-(4-(trifluoromethoxy)phenyl)methyl]amino]acetyl]amino}phenyl]ethynyl]benzamide	585.5
880		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[[4-[[[4-(4-(methylthio)phenyl)methyl]amino]acetyl]amino}phenyl]ethynyl]benzamide	547.6
881		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[[4-[[[4-(4-(trifluoromethylthio)phenyl)methyl]amino]acetyl]amino}phenyl]ethynyl]benzamide	601.6
882		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[[4-[[[4-(4-(methylsulfonyl)phenyl)methyl]amino]acetyl]amino}phenyl]ethynyl]benzamide	579.6
883		4-((4-[[[2,5-difluorophenyl]methyl]amino]acetyl]amino}phenyl]ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	537.5
884		4-1-((4-[[[2,6-difluorophenyl]methyl]amino]acetyl]amino}phenyl]ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	537.5

(continued)

Example	Structure	Name	MH+
885		4-({4-([[(3,4-difluorophenyl)methyl]amino)acetyl]amino]phenyl}ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	537.5
886		4-({4-([[(3,4-dichlorophenyl)methyl]amino)acetyl]amino]phenyl}ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	570.4
887		4-({4-([[(3,4-dimethylphenyl)methyl]amino)acetyl]amino]phenyl}ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	529.6
888		4-({4-([[(3,5-dichlorophenyl)methyl]amino)acetyl]amino]phenyl}ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	570.4
889		4-L-4-([[(3,5-bis(trifluoromethyl)phenyl)methyl]amino)acetyl]amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	637.5
890		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-({4-([[(2,3,4-trifluorophenyl)methyl]amino)acetyl]amino]phenyl}ethynyl)benzamide	555.5
891		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-({4-([[(2,4,5-trifluorophenyl)methyl]amino)acetyl]amino]phenyl}ethynyl)benzamide	555.5
892		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-({4-([[(3,4,5-trifluorophenyl)methyl]amino)acetyl]amino]phenyl}ethynyl)benzamide	555.5
925*		N-[(1S)-1-(aminomethyl)-2-(hydroxyamino)-2-oxoethyl]-4-({4-([[(4-methylphenyl)methyl]amino)acetyl]amino]phenyl)buta-1,3-diynyl)benzamide	524.6
973		4-[(6-chloropyridin-3-yl)ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	374.8
Examples	Structure	Name	MH+
997		4-[(4-([[(2S)-2-amino-3-(4-aminophenyl)propanoyl]amino]phenyl)ethynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	516.6

(continued)

Examples	Structure	Name	MH+
998		4-((2S)-2-amino-3-((4-((4-(((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)amino)carbonyl]phenyl) ethynyl)phenyl)amino)-3-oxopropyl)benzoic acid	545.6
1000		N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)-4-((4-(((1-(hydroxymethyl)-2-methylpropyl)amino]acetyl)amino)phenyl)ethynyl)benzamide	497.6
Example	Structure	Name	MH+
1001		4-[4-(3-aminophenyl)buta-1,3-diynyl]-N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl) benzamide	378.4
1012		4-[4-(4-(((2S)-2-amino-3-oxopropanoyl)amino)phenyl)buta-1,3-diynyl]-N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)benzamide	449.5
1017		4-[(4-(((2S)-2-amino-3-(4-hydroxyphenyl)propanoyl)amino)phenyl)ethynyl]-N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl) benzamide	517.6
1018		4-(4-(4-((aminoacetyl)amino)phenyl)buta-1,3-diynyl)-N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)benzamide	435.4
1022		N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)-4-((4-((methylsulfonyl)amino)phenyl)ethynyl)benzamide	432.5
1033		N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl)-4-(4-(4-(((6-(methyloxy)pyridin-3-yl)amino)acetyl)amino)phenyl)buta-1,3-diynyl) benzamide	542.6
1034		4-[4-(4-(((6-chloropyridin-3-yl)amino)acetyl)amino)phenyl]buta-1,3-diynyl)-N-((1S,2R)-2-hydroxy-1-((hydroxyamino)carbonyl)propyl) benzamide	547.0

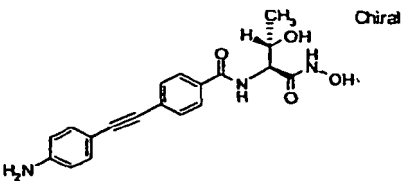
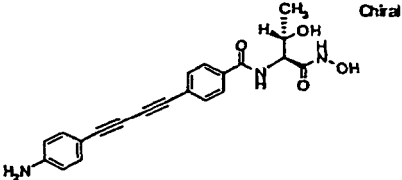
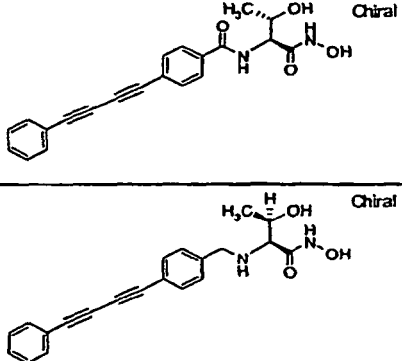
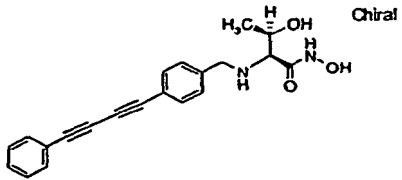
(continued)

Example	Structure	Name	MH+
1042		4-[4-(2-aminophenyl)buta-1,3-diynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	378.4
1045		4-[4-(4-[(2S)-2-amino-4-methylpentanoyl]amino)phenyl]buta-1,3-diynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	491.6
1046		(2S)-N-[4-(4-{4-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]amino}carbonyl]phenyl]buta-1,3-diynyl]phenyl]pyrrolidine-2-carboxamide	475.5
1047		(2S)-N-[4-(4-{4-[(1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]amino}carbonyl]phenyl]buta-1,3-diynyl]phenyl]piperidine-2-carboxamide	489.5
1048		4-[4-(4-[(2S)-2,3-diaminopropanoyl]amino)phenyl]buta-1,3-diynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	464.5
1049		4-[4-(4-[(2S)-2-amino-3-(1H-imidazol-4-yl)propanoyl]amino)phenyl]buta-1,3-diynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	515.5
1065		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[4-(3-hydroxyphenyl)buta-1,3-diynyl]benzamide	379.4
1083		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-0-(4-[4-[(methylsulfonyl)amino]phenyl]buta-1,3-diynyl)benzamide	456.5
1084		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[4-(3-[(methylsulfonyl)amino]phenyl)buta-1,3-diynyl]benzamide	456.5
1086		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-[4-(3-nitrophenyl)buta-1,3-diynyl]benzamide	408.4
1236		4-[4-(3-amino-4-methylphenyl)buta-1,3-diynyl]-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)benzamide	392.4

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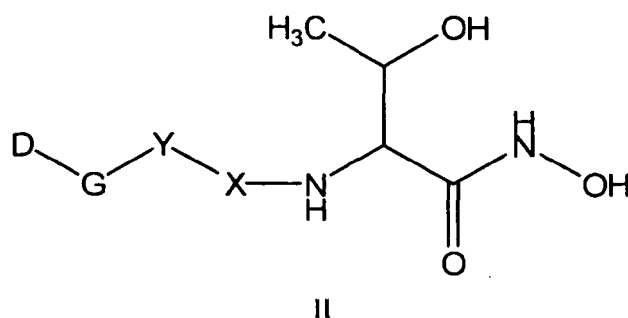
Example	Structure	Name	MH+
1246		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-([methyl(pyridin-2-ylmethyl)amino]acetyl)amino]phenyl)ethynyl}benzamide	516.6
1247		4-([4-([[(2-fluorophenyl)methyl](methyl)amino]acetyl)amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl}benzamide	533.6
1248		4-([4-([[(3-fluorophenyl)methyl](methyl)amino]acetyl)amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl}benzamide	533.6
1249		4-([4-([[(4-fluorophenyl)methyl](methyl)amino]acetyl)amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl}benzamide	533.6
1256		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-([methyl(propyl)amino]acetyl)amino]phenyl)ethynyl}benzamide	467.5
1257		4-([4-([butyl(methyl)amino]acetyl)phenyl]ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl}benzamide	481.6
1258		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-([methyl(pentyl)amino]acetyl)amino]phenyl)ethynyl}benzamide	495.6
1259		4-([4-([hexyl(methyl)amino]acetyl)amino]phenyl)ethynyl)-N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl}benzamide	509.6
1260		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-([methyl(1-methylethyl)amino]acetyl)amino]phenyl)ethynyl}benzamide	467.5
1261		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-([methyl(2-methylpropyl)amino]acetyl)amino]phenyl)ethynyl}benzamide	481.6
1262		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-4-([4-([methyl[(2-methylphenyl)methyl]amino]acetyl)amino]phenyl)ethynyl}benzamide	529.6
1263		N-((1S,2R)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl)-0-([4-([methyl[(4-methylphenyl)methyl]amino]acetyl)amino]phenyl)ethynyl}benzamide	529.6
1273		4-([4-([[(2S)-2-aminopropanoyl]amino]phenyl)ethynyl)-N-((1S,2S)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl}benzamide	425.5

(continued)

Example	Structure	Name	MH+
1285		4-[(4-aminophenyl)ethynyl]-N-[(1S,2S)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	354.4
1286		4-[4-(4-aminophenyl)buta-1,3-diynyl]-N-[(1S,2S)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]benzamide	378.4
1302		N-[(1S,2S)-2-hydroxy-1-[(hydroxyamino)carbonyl]propyl]-4-(4-phenylbuta-1,3-diynyl)benzamide	363.4
1303		(2S,3R)-N,3-dihydroxy-2-[[4-(4-phenylbuta-1,3-diynyl)phenyl]methyl]ammoniumbutanamide	349.4

## Claims

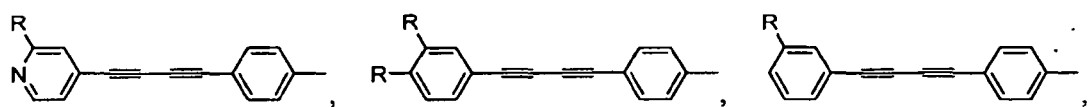
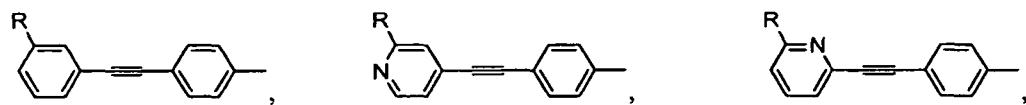
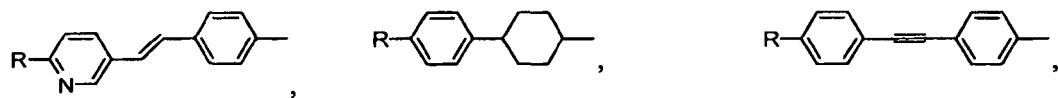
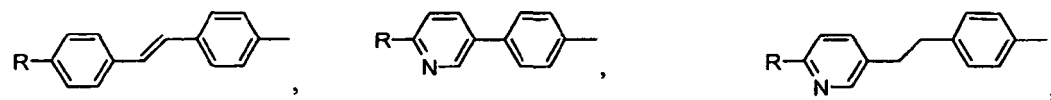
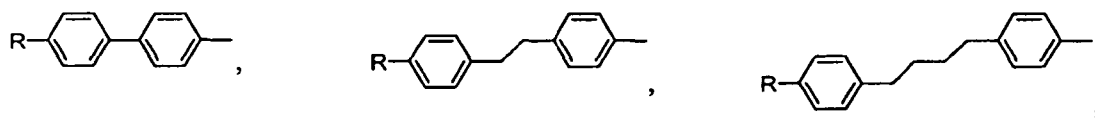
1. A compound, having the formula II:



or a stereoisomer, pharmaceutically acceptable salt, or ester thereof, wherein

D-G-Y taken together, is selected from the group consisting of

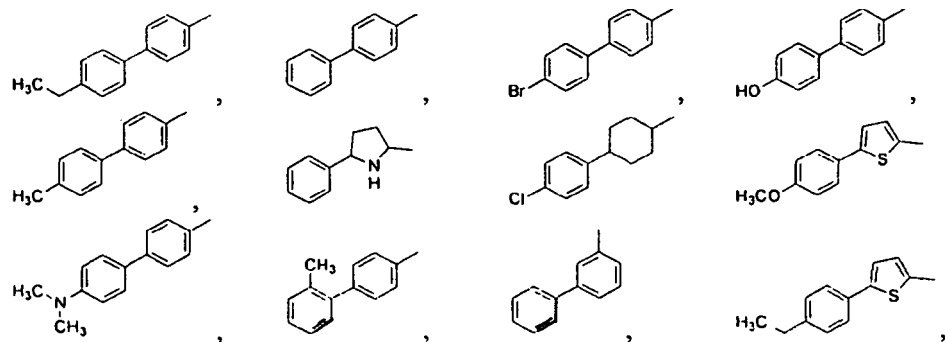


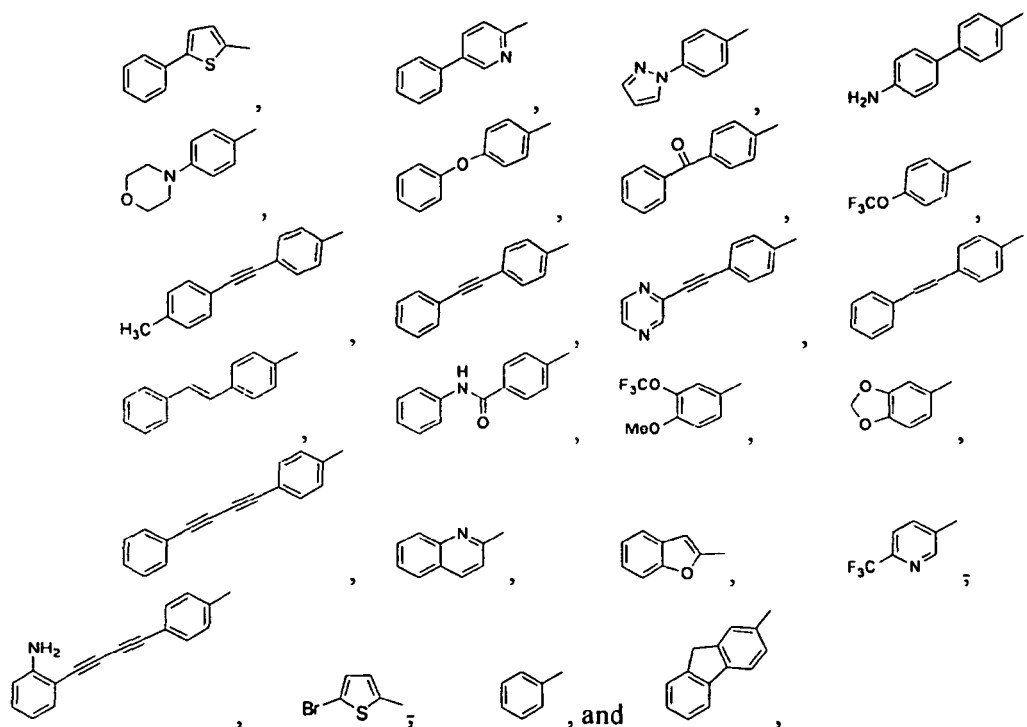


and



or





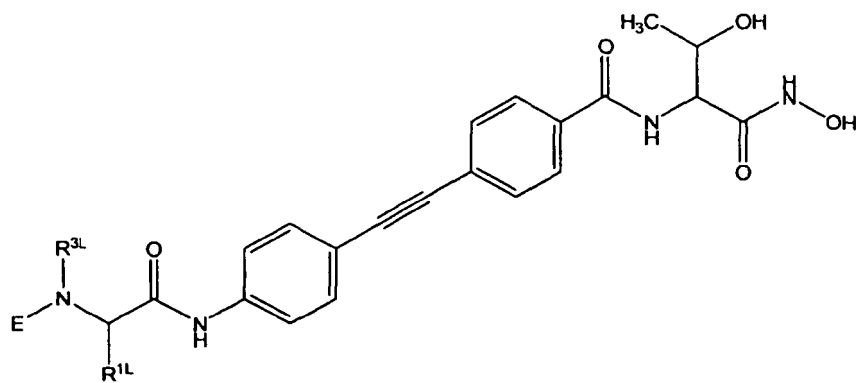
wherein

R is selected from the group consisting of -CH<sub>3</sub>, -C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>OH, -OH, -OCH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, -OCF<sub>3</sub>, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>H, -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, -NH<sub>2</sub>, -F, -Cl, -Br, -CF<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -NHSO<sub>2</sub>CH<sub>3</sub>, and -NHCOCH<sub>3</sub>; and

X is selected from the groups consisting of

- (1) -(C=O)-,
- (2) -C<sub>1</sub>-C<sub>6</sub>-alkyl-(C=O)-, and
- (3) -C<sub>2</sub>-C<sub>6</sub>-alkenyl-(C=O)-.

**2. A compound having the formula VI:**



VI

or a stereoisomer, pharmaceutically acceptable salt, or ester thereof, wherein E is absent or selected from the group consisting of

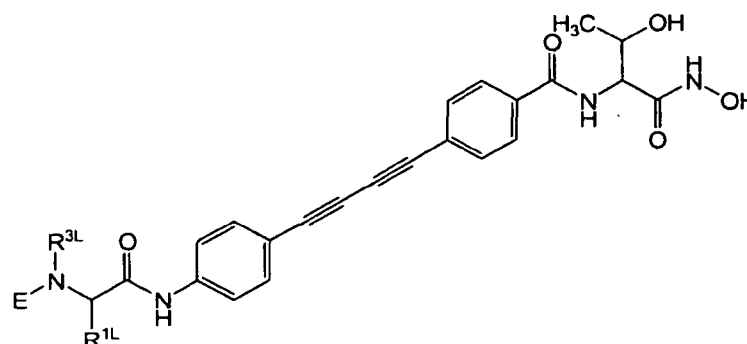
- (1) H,
- (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
- (3) substituted or unsubstituted aryl,
- (4) substituted or unsubstituted heterocyclyl, and

(5) substituted or unsubstituted heteroaryl,  
or E and R<sup>3L</sup> together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 10 ring atoms, wherein 1-4 ring atoms of the heterocyclic ring system are selected from N, O and S;

R<sup>1L</sup>, R<sup>3L</sup> are independently selected from the group consisting of

- (1) H,
  - (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
  - (3) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with aryl,
  - (4) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heterocyclyl, and
  - (5) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heteroaryl,
- or R<sup>1L</sup> and R<sup>3L</sup> together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S, wherein alkyl includes straight chain, branched chain and cyclic alkyl groups.

3. A compound having the formula VIII:



VIII

or a stereoisomer, pharmaceutically acceptable salt, or ester, wherein E is absent or selected from the group consisting of

- (1) H,
  - (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
  - (3) substituted or unsubstituted aryl,
  - (4) substituted or unsubstituted heterocyclyl, and
  - (5) substituted or unsubstituted heteroaryl,
- or E and R<sup>3L</sup> together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 10 ring atoms, wherein 1-4 ring atoms of the heterocyclic ring system are selected from N, O and S;

R<sup>1L</sup>, R<sup>3L</sup> are independently selected from the group consisting of

- (1) H,
- (2) substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub>-alkyl,
- (3) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with aryl,
- (4) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heterocyclyl, and
- (5) C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with heteroaryl,

or R<sup>1L</sup> and R<sup>3L</sup>, together with the atoms to which they are attached can form a substituted or unsubstituted heterocyclic ring, having from 3 to 8 ring atoms, wherein 1-2 ring atoms of the heterocyclic ring system are selected from N, O and S, wherein alkyl includes straight chain, branched chain and cyclic alkyl groups.

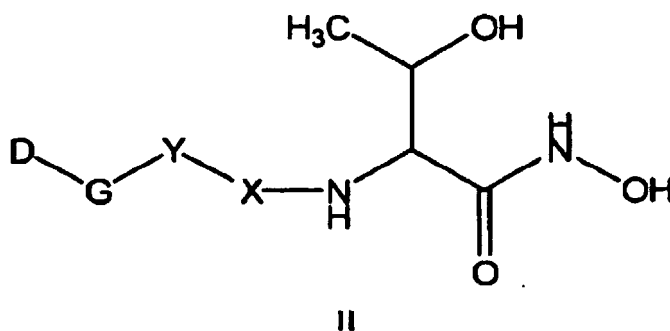
4. A pharmaceutical composition comprising a compound from one of claims 1-3 and a pharmaceutically acceptable

excipient.

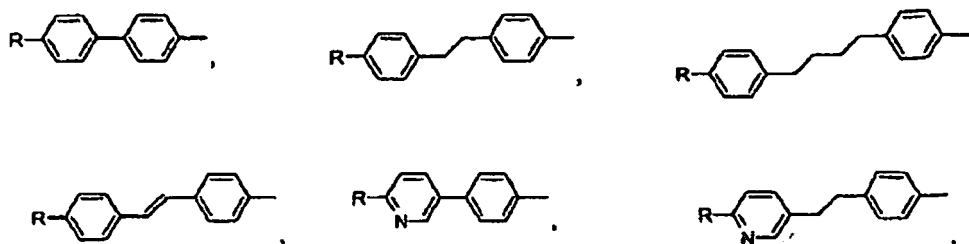
5. A pharmaceutical composition comprising a compound from one of claims 1-3, a second agent, and a pharmaceutically acceptable excipient, wherein the second agent is an antibacterial agent; an antiendotoxin agent for the treatment of sepsis, septic shock, systemic inflammation, localized inflammation, chronic obstructive pulmonary disease or acute exacerbations of chronic bronchitis; or an inhaled non-antibacterial agent for the treatment of serious or chronic respiratory tract infection.
6. A pharmaceutical composition as claimed in claim 4 for use in treating an infection.
7. A pharmaceutical composition as claimed in claim 5 for use in treating an infection.
8. Use of a compound from one of claims 1 - 3 in the manufacture of a medicament for treating a bacterial infection.
9. Use of a compound from one of claims 1 - 3 in the manufacture of a medicament for treating a bacterial infection in conjunction with a second agent, wherein the second agent is an antibacterial agent; an antiendotoxin agent, for the treatment of sepsis, septic shock, systemic inflammation, localized inflammation, chronic obstructive pulmonary disease or acute exacerbations of chronic bronchitis or an inhaled non-antibacterial agent for the treatment of serious or chronic respiratory tract infection
10. A compound from one of claims 1 - 3 for use in a method of treating a bacterial infection.
11. A compound from one of claims 1 - 3 for use in a method of treating a bacterial infection in conjunction with a second agent, wherein the second agent is an antibacterial agent; an antiendotoxin agent, for the treatment of sepsis, septic shock, systemic inflammation, localized inflammation, chronic obstructive pulmonary disease or acute exacerbations of chronic bronchitis or an inhaled non-antibacterial agent for the treatment of serious or chronic respiratory tract infection

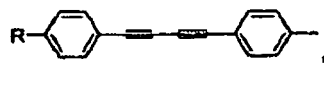
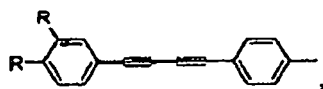
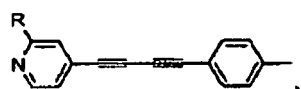
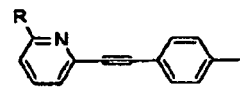
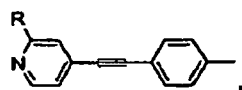
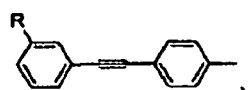
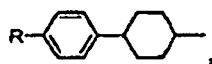
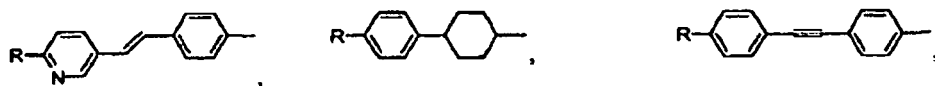
## Patentansprüche

1. Verbindung der Formel II:

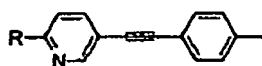


oder ein Stereoisomer, ein pharmazeutisch unbedenkliches Salz oder ein Ester davon, worin D-G-Y zusammengekommen aus der Gruppe bestehend aus

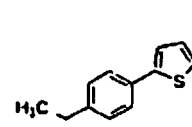
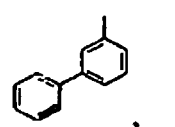
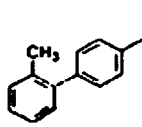
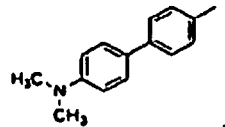
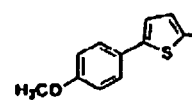
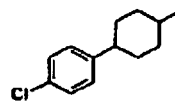
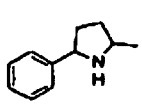
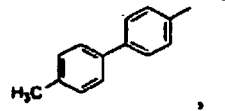
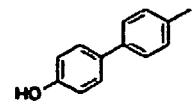
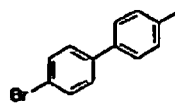
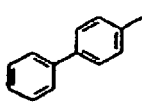
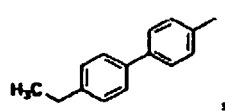


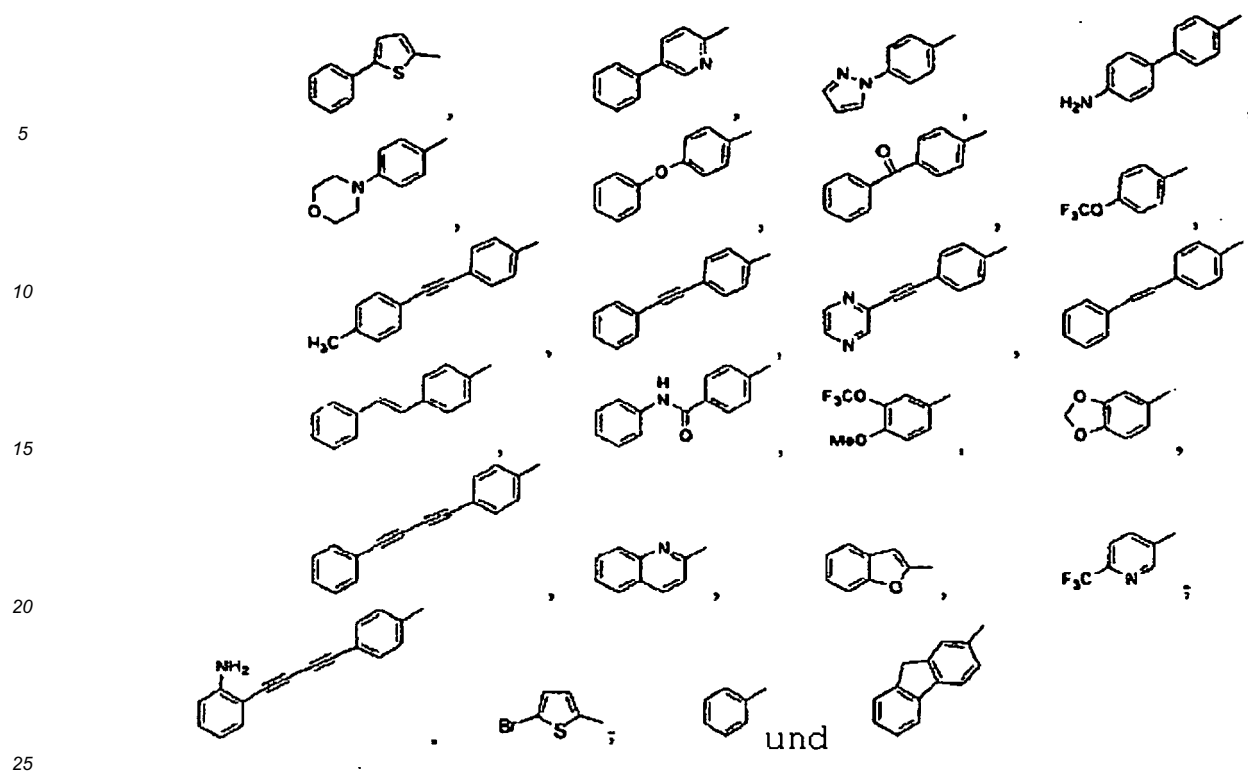


und



oder





ausgewählt ist,

worin

R aus der Gruppe bestehend aus -CH<sub>3</sub>, -C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>OH,

- OH, -OCH<sub>3</sub>, -OC<sub>2</sub>H<sub>5</sub>, -OCF<sub>3</sub>, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>H, -CO<sub>2</sub>CH<sub>3</sub>,

- CONH<sub>2</sub>, -NH<sub>2</sub>, -F, -Cl, -Br, -CF<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -NHSO<sub>2</sub>CH<sub>3</sub> und -NHCOCH<sub>3</sub> ausgewählt ist und

X aus den Gruppen bestehend aus

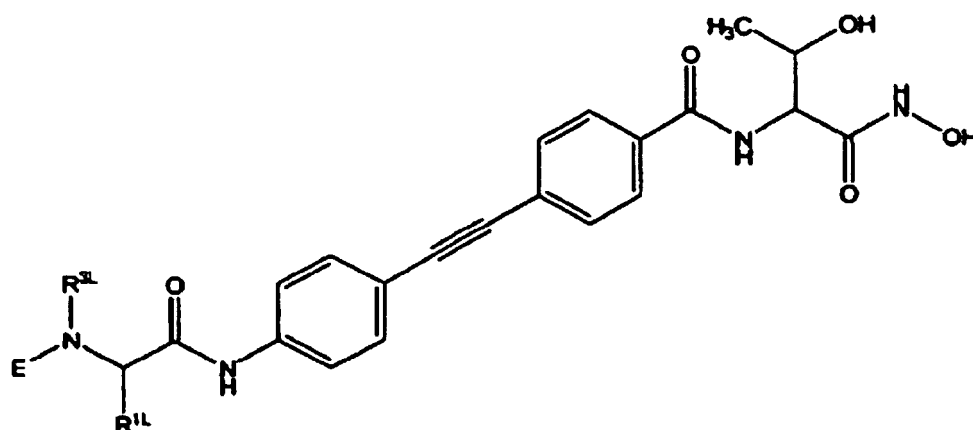
(1)  $-(\text{C}=\text{O})-$ ,

(2) -C<sub>1</sub>-C<sub>6</sub>-Aaryl-(C=O)- und

(3) -C<sub>2</sub>-C<sub>6</sub>-Alkenyl-(C=O)-

ausgewählt ist.

## 2. Verbindung der Formel VI:



VI

oder ein Stereoisomer, ein pharmazeutisch unbedenkliches Salz oder ein Ester davon, worin E fehlt oder aus der Gruppe bestehend aus

- (1) H,
- (2) substituiertem oder unsubstituiertem C<sub>1</sub>-C<sub>6</sub>-Alkyl,
- (3) substituiertem oder unsubstituiertem Aryl,
- (4) substituiertem oder unsubstituiertem Heterocyclyl und
- (5) substituiertem oder unsubstituiertem Heteroaryl

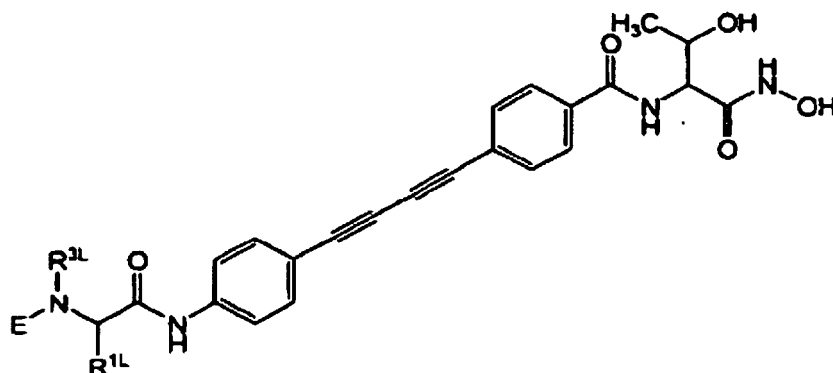
ausgewählt ist oder E und R<sup>3L</sup> zusammen mit den Atomen, an die sie gebunden sind, einen substituierten oder unsubstituierten heterocyclischen Ring mit 3 bis 10 Ringatomen bilden können, wobei 1-4 Ringatome des heterocyclischen Ringsystems aus N, O und S ausgewählt sind;

R<sup>1L</sup> und R<sup>3L</sup> unabhängig voneinander aus der Gruppe bestehend aus

- (1) H,
- (2) substituiertem oder unsubstituiertem C<sub>1</sub>-C<sub>6</sub>-Alkyl,
- (3) durch Aryl substituiertem C<sub>1</sub>-C<sub>6</sub>-Alkyl,
- (4) durch Heterocyclyl substituiertem C<sub>1</sub>-C<sub>6</sub>-Alkyl
- und
- (5) durch Heteroaryl substituiertem C<sub>1</sub>-C<sub>6</sub>-Alkyl ausgewählt sind oder R<sup>1L</sup> und R<sup>3L</sup> zusammen mit den Atomen, an die sie gebunden sind, einen substituierten oder unsubstituierten heterocyclischen Ring mit 3 bis 8 Ringatomen bilden können, wobei 1-2 Ringatome des heterocyclischen Ringsystems aus N,

O und S ausgewählt sind; wobei Alkyl geradkettige, verzweigt-kettige und cyclische Alkylgruppen einschließt.

### 3. Verbindung der Formel VIII:



## VIII

oder ein Stereoisomer, ein pharmazeutisch unbedenkliches Salz oder ein Ester davon, worin E fehlt oder aus der Gruppe bestehend aus

- (1) H,
- (2) substituiertem oder unsubstituiertem C<sub>1</sub>-C<sub>6</sub>-Alkyl,
- (3) substituiertem oder unsubstituiertem Aryl,
- (4) substituiertem oder unsubstituiertem Heterocyclyl und
- (5) substituiertem oder unsubstituiertem Heteroaryl

ausgewählt ist oder E und R<sup>3L</sup> zusammen mit den Atomen, an die sie gebunden sind, einen substituierten oder unsubstituierten heterocyclischen Ring mit 3 bis 10 Ringatomen bilden können, wobei 1-4 Ringatome des heterocyclischen Ringsystems aus N, O und S ausgewählt sind;

R<sup>1L</sup> und R<sup>3L</sup> unabhängig voneinander aus der Gruppe bestehend aus

- (1) H,
- (2) substituiertem oder unsubstituiertem C<sub>1</sub>-C<sub>6</sub>-Alkyl,
- (3) durch Aryl substituiertem C<sub>1</sub>-C<sub>6</sub>-Alkyl,
- (4) durch Heterocyclyl substituiertem C<sub>1</sub>-C<sub>6</sub>-Alkyl
- und
- (5) durch Heteroaryl substituiertem C<sub>1</sub>-C<sub>6</sub>-Alkyl ausgewählt sind oder R<sup>1L</sup> und R<sup>3L</sup> zusammen mit den Atomen, an die sie gebunden sind, einen substituierten oder unsubstituierten heterocyclischen Ring mit 3 bis 8 Ringatomen bilden können, wobei 1-2 Ringatome des heterocyclischen Ringsystems aus N,

O und S ausgewählt sind; wobei Alkyl geradkettige, verzweigt-kettige und cyclische Alkylgruppen einschließt.

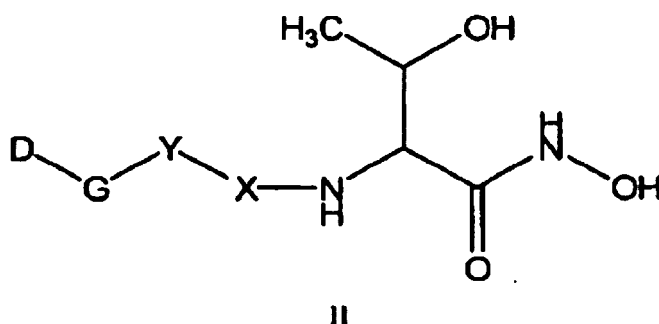
4. Pharmazeutische Zusammensetzung, umfassend eine Verbindung aus einem der Ansprüche 1-3 und einen pharmazeutisch unbedenklichen Hilfsstoff.
5. Pharmazeutische Zusammensetzung, umfassend eine Verbindung aus einem der Ansprüche 1-3, ein zweites Mittel und einen pharmazeutisch unbedenklichen Hilfsstoff, wobei es sich bei dem zweiten Mittel um ein antibakterielles Mittel; ein Antiendotoxinmittel zur Behandlung von Sepsis, septischem Schock, systemischer Entzündung, lokalisierter Entzündung, chronisch-obstruktiver Lungenerkrankung oder akuten Verschlimmerungen von chronischer Bronchitis oder ein inhaliertes nichtantibakterielles Mittel zur Behandlung von schwerer oder chronischer Atemwegsinfektion handelt.
6. Pharmazeutische Zusammensetzung nach Anspruch 4 zur Verwendung bei der Behandlung einer Infektion.
7. Pharmazeutische Zusammensetzung nach Anspruch 5 zur Verwendung bei der Behandlung einer Infektion.
8. Verwendung einer Verbindung aus einem der Ansprüche 1-3 bei der Herstellung eines Arzneimittels zur Behandlung einer bakteriellen Infektion.



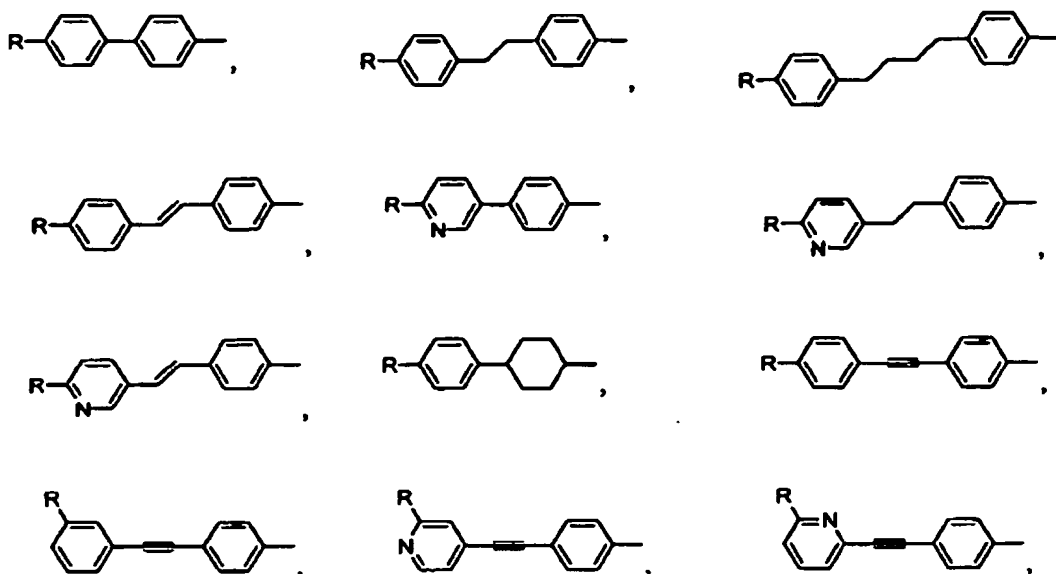
9. Verwendung einer Verbindung aus einem der Ansprüche 1-3 bei der Herstellung eines Arzneimittels zur Behandlung einer bakteriellen Infektion in Verbindung mit einem zweiten Mittel, wobei es sich bei dem zweiten Mittel um ein antibakterielles Mittel; ein Antiendotoxinmittel zur Behandlung von Sepsis, septischem Schock, systemischer Entzündung, lokalisierter Entzündung, chronisch-obstruktiver Lungenerkrankung oder akuten Verschlimmerungen von chronischer Bronchitis oder ein inhaliertes nichtantibakterielles Mittel zur Behandlung von schwerer oder chronischer Atemwegsinfektion handelt.
10. Verbindung aus einem der Ansprüche 1-3 zur Verwendung bei einem Verfahren zur Behandlung einer bakteriellen Infektion.
11. Verbindung aus einem der Ansprüche 1-3 zur Verwendung bei einem Verfahren zur Behandlung einer bakteriellen Infektion in Verbindung mit einem zweiten Mittel, wobei es sich bei dem zweiten Mittel um ein antibakterielles Mittel; ein Antiendotoxinmittel zur Behandlung von Sepsis, septischem Schock, systemischer Entzündung, lokalisierter Entzündung, chronisch-obstruktiver Lungenerkrankung oder akuten Verschlimmerungen von chronischer Bronchitis oder ein inhaliertes nichtantibakterielles Mittel zur Behandlung von schwerer oder chronischer Atemwegsinfektion handelt.

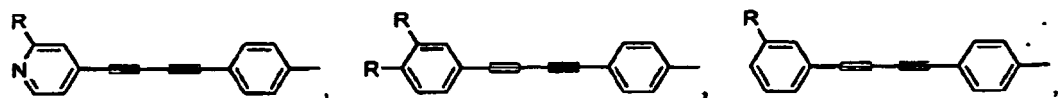
# Revendications

1. Composé répondant à la formule II :

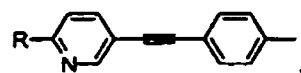


ou un stéréoisomère, un sel pharmaceutiquement acceptable ou un ester de celui-ci, dans laquelle D-G-Y pris ensemble, est choisi dans le groupe constitué par

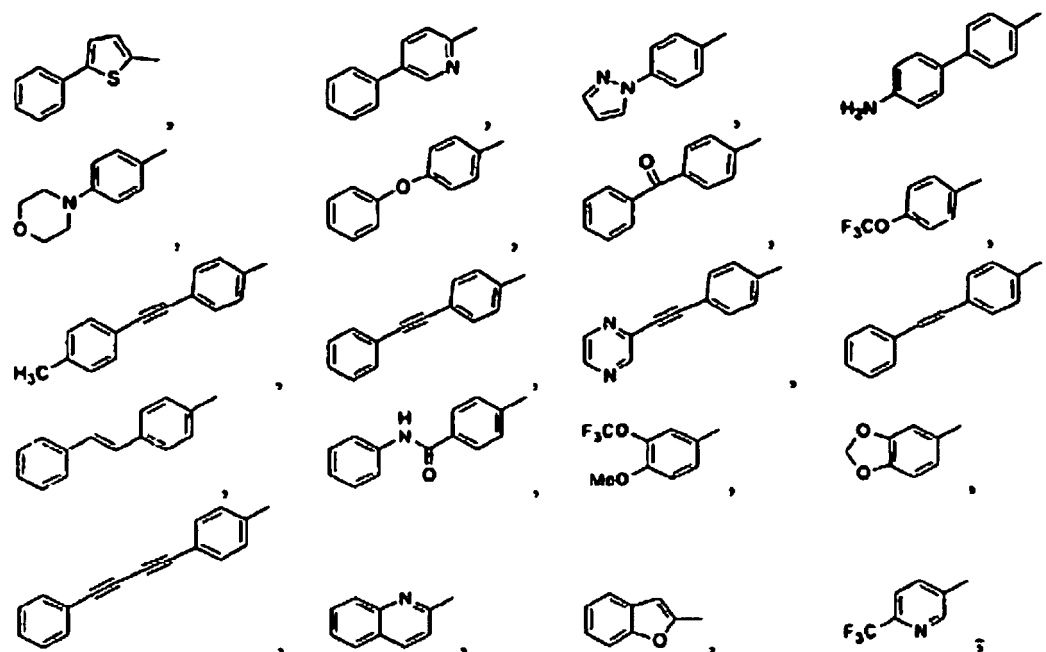
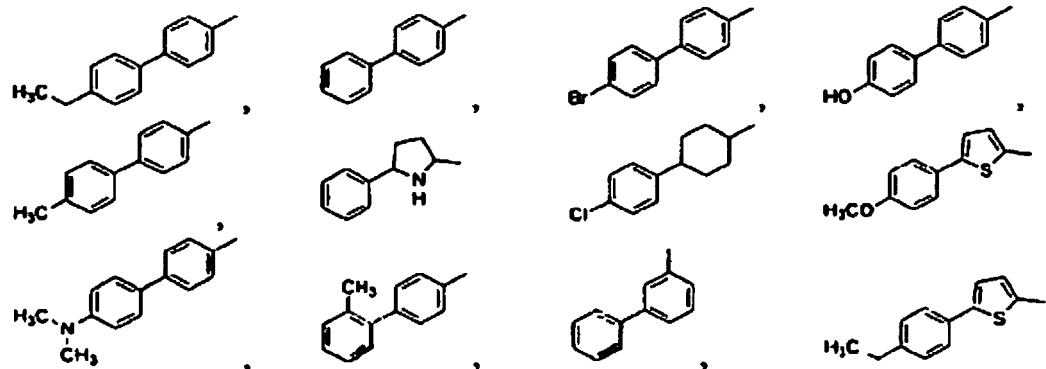


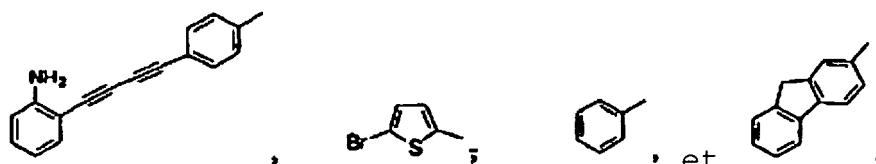


et



OU





où

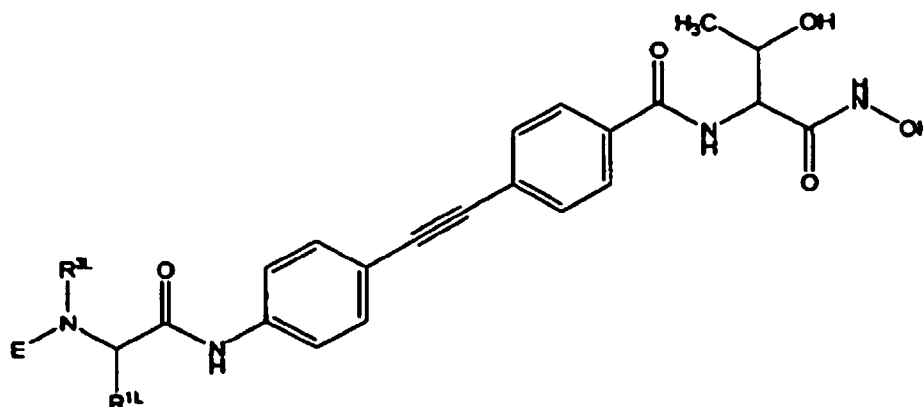
R est choisi dans le groupe constitué par -CH<sub>3</sub>, -C<sub>2</sub>H<sub>5</sub>,

- CH<sub>2</sub>OH, -OH, -OCH<sub>3</sub>, -OC<sub>2</sub>H<sub>5</sub>, -OCF<sub>3</sub>, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>H,
- CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, -NH<sub>2</sub>, -F, -Cl, -Br, -CF<sub>3</sub>, -N(CH<sub>3</sub>)<sub>2</sub>,
- NHSO<sub>2</sub>CH<sub>3</sub> et -NHCOCH<sub>3</sub> ; et

X est choisi dans les groupes constitués par

- (1) -(C=O)-,
- (2) -C<sub>1</sub>-C<sub>6</sub>-alkyl- (C=O) -, et
- (3) -C<sub>2</sub>-C<sub>6</sub>-alcényl-(C=O)-.

## 2. Composé répondant à la formule VI :



VI

ou un stéréoisomère, un sel pharmaceutiquement acceptable ou un ester de celui-ci, dans laquelle E est absent ou est choisi dans le groupe constitué par

- (1) H,
- (2) C<sub>1</sub>-C<sub>6</sub>-alkyle substitué ou non substitué,
- (3) aryle substitué ou non substitué,
- (4) hétérocyclyle substitué ou non substitué, et
- (5) hétéroaryle substitué ou non substitué,

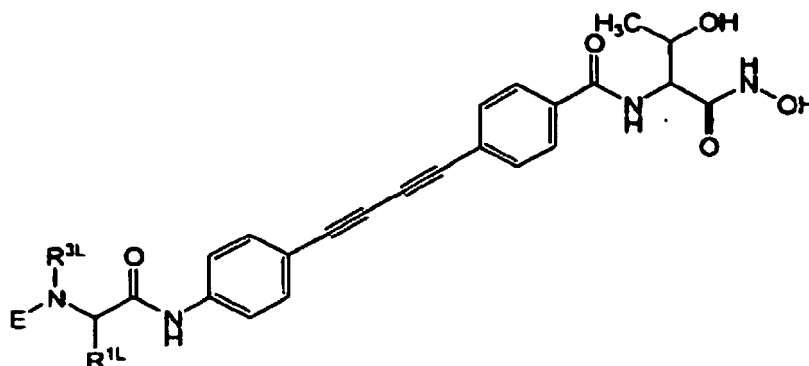
ou E et R<sup>3L</sup>, conjointement avec les atomes auxquels ils sont fixés, peuvent former un cycle hétérocyclique substitué ou non substitué, ayant de 3 à 10 atomes de cycle, où 1-4 atomes de cycle du noyau hétérocyclique sont choisis parmi N, O et S ;

R<sup>1L</sup> et R<sup>3L</sup> sont choisis indépendamment dans le groupe constitué par

- (1) H,
- (2) C<sub>1</sub>-C<sub>6</sub>-alkyle substitué ou non substitué,
- (3) C<sub>1</sub>-C<sub>6</sub>-alkyle substitué par aryle,
- (4) C<sub>1</sub>-C<sub>6</sub>-alkyle substitué par hétérocyclyle, et
- (5) C<sub>1</sub>-C<sub>6</sub>-alkyle substitué par hétéroaryle,

ou R<sup>1L</sup> et R<sup>3L</sup>, conjointement avec les atomes auxquels ils sont fixés, peuvent former un cycle hétérocyclique substitué ou non substitué, ayant de 3 à 8 atomes de cycle, où 1-2 atomes de cycle du noyau hétérocyclique sont choisis parmi N, O et S, où alkyle comporte les groupements alkyle à chaîne linéaire, à chaîne ramifiée et cycliques.

3. Composé répondant à la formule VIII:



VIII

ou un stéréoisomère, un sel pharmaceutiquement acceptable ou un ester de celui-ci, dans laquelle E est absent ou est choisi dans le groupe constitué par

- (1) H,
- (2) C<sub>1</sub>-C<sub>6</sub>-alkyle substitué ou non substitué,
- (3) aryle substitué ou non substitué,
- (4) hétérocyclyle substitué ou non substitué, et
- (5) hétéroaryle substitué ou non substitué,

ou E et R<sup>3L</sup>, conjointement avec les atomes auxquels ils sont fixés, peuvent former un cycle hétérocyclique substitué ou non substitué, ayant de 3 à 10 atomes de cycle, où 1-4 atomes de cycle du noyau hétérocyclique sont choisis parmi N, O et S ;

R<sup>1L</sup> et R<sup>3L</sup> sont choisis indépendamment dans le groupe constitué par

- (1) H,
- (2) C<sub>1</sub>-C<sub>6</sub>-alkyle substitué ou non substitué,
- (3) C<sub>1</sub>-C<sub>6</sub>-alkyle substitué par aryle,
- (4) C<sub>1</sub>-C<sub>6</sub>-alkyle substitué par hétérocyclyle, et
- (5) C<sub>1</sub>-C<sub>6</sub>-alkyle substitué par hétéroaryle,

ou R<sup>1L</sup> et R<sup>3L</sup>, conjointement avec les atomes auxquels ils sont fixés, peuvent former un cycle hétérocyclique substitué ou non substitué, ayant de 3 à 8 atomes de cycle, où 1-2 atomes de cycle du noyau hétérocyclique sont choisis parmi N, O et S, où alkyle comporte les groupements alkyle à chaîne linéaire, à chaîne ramifiée et cycliques.

4. Composition pharmaceutique comprenant un composé selon l'une des revendications 1-3 et un excipient pharmaceutiquement acceptable.
5. Composition pharmaceutique comprenant un composé selon l'une des revendications 1-3, un deuxième agent, et un excipient pharmaceutiquement acceptable, dans laquelle le deuxième agent est un agent antibactérien ; un agent anti-endotoxine destiné au traitement de la sepsie, du choc septique, des inflammations systémiques, des inflammations localisées, de la broncho-pneumopathie chronique obstructive ou des exacerbations aiguës de la bronchite chronique ; ou un agent non antibactérien inhalé destiné au traitement d'infections sérieuses ou chroniques du tractus respiratoire.
6. Composition pharmaceutique selon la revendication 4, pour une utilisation dans le traitement d'une infection.
7. Composition pharmaceutique selon la revendication 5, pour une utilisation dans le traitement d'une infection.

8. Utilisation d'un composé selon l'une des revendications 1-3, dans l'élaboration d'un médicament destiné à traiter une infection bactérienne.

9. Utilisation d'un composé selon l'une des revendications 1-3, dans l'élaboration d'un médicament destiné à traiter une infection bactérienne, conjointement avec un deuxième agent, où le deuxième agent est un agent antibactérien ; un agent anti-endotoxine destiné au traitement de la sepsie, du choc septique, des inflammations systémiques, des inflammations localisées, de la broncho-pneumopathie chronique obstructive ou des exacerbations aiguës de la bronchite chronique ; ou un agent non antibactérien inhalé destiné au traitement d'infections sérieuses ou chroniques du tractus respiratoire.

10. Composé selon l'une des revendications 1-3, pour une utilisation dans une méthode de traitement d'une infection bactérienne.

11. Composé selon l'une des revendications 1-3, pour une utilisation dans une méthode de traitement d'une infection bactérienne conjointement avec un deuxième agent, où le deuxième agent est un agent antibactérien ; un agent anti-endotoxine destiné au traitement de la sepsie, du choc septique, des inflammations systémiques, des inflammations localisées, de la broncho-pneumopathie chronique obstructive ou des exacerbations aiguës de la bronchite chronique ; ou un agent non antibactérien inhalé destiné au traitement d'infections sérieuses ou chroniques du tractus respiratoire.

## REFERENCES CITED IN THE DESCRIPTION

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